Is Migraine Surgery Ready for Prime Time? The Surgical Team's View

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Background.—Based on unsolicited reports by patients that their headaches had ceased or reduced following forehead rejuvenation, our team began stepwise and logical studies to investigate the efficacy of surgery as a potential preventive modality for selected patients with migraine headaches (MH). The purpose of this report is to summarize the pertinent studies demonstrating the efficacy of surgical decompression trigger sites of migraine trigger sites.

Methods.—These studies included a retrospective, a prospective pilot, a prospective randomized study with a control arm, a prospective randomized study with sham surgery, and a 5-year follow-up. There were 3 reputable and respected neurologists who specialize in headaches, an expert biostatistician, 13 residents, and 10 medical students involved in these studies.

Results.—In our retrospective study, of the 249 patients, 39 confirmed having MH prior to the surgery, and 31 ($P<.0001$) experienced either complete elimination or significant improvement (at least 50% reduction) of their MH. In our prospective pilot study, 21 of the 22 patients noted a significant improvement ($P<.001$). In our prospective randomized study, 82 of 89 (92%) observed at least 50% improvement in the frequency, intensity, and duration of MH ($P<.00001$). Sixty-one of 69 (88%) patients in this study who were followed for 5 years persisted to have significant improvement after 5 years ($P<.0001$). In our randomized study involving sham surgery, 21 of the 49 (83%) patients benefitted from the real surgery compared to 15 of 26 (56%) patients in the sham surgery group ($P=.014$). While 28 (57%) patients in the real surgery group observed complete elimination, only 1 patient in the sham surgery group reported elimination ($P<.0001$).

Conclusions.—This report discusses the facts surrounding the discovery of this surgery, demonstrates accuracy of our studies and effectiveness of the proposed surgeries and dispels some of the unfounded assertions trying to discredit the research that we have conducted over 14 years.

Key words: migraine, migraine surgery, trigger

Abbreviation: MH migraine headache

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Accepted for publication September 13, 2015.

Headache

INTRODUCTION

Plastic surgeons were not looking for a surgical treatment for migraine headaches (MH). The idea for surgery began with patients reporting that their headaches were disappearing after forehead rejuvenation plastic surgery in 1999. This was the first evidence against the subsequent repeated claims by Professor H-C Diener[1] that the improvement in MH following nerve decompression is a placebo effect. Neither the patients nor the surgeons were anticipating such a response, and this type of connection between forehead surgery and MH was not anticipated, thus it cannot be considered the consequence of a placebo effect at that time.

Overall, we have published 24 clinical and anatomical articles related to this topic in highly reputable peer reviewed journals.[2–23] Currently, we have 13 additional studies in various stages of completion, demonstrating our team's unwavering commitment to improvement of our results and our firm conviction that this surgery is benefiting properly selected patients. Three other centers have conducted totally independent retrospective reviews of their results, which confirmed the efficacy of surgical decompression of MH trigger sites.[24–26]

The purpose of this report is to summarize the exhaustive investigations done by our team demonstrating the effectiveness of the peripheral nerve surgery that we developed for decompression or deactivation of migraine trigger sites and to respond to Professor Diener's allegations that our studies are fraught with flaws. His repeated contention is that the positive reports by the patients are a placebo effect, and I will offer sufficient evidence against these unfounded accusations for any fair and open-minded reader.

THE FIRST RETROSPECTIVE STUDY

Intrigued by the observation made by patients whose headaches stopped after forehead rejuvenation plastic surgery, yet highly skeptical of the connection, we conducted a retrospective study to investigate whether the phenomenon that the patients noted was a coincidence or whether there was a potential association.

Methods

Questionnaires were sent to the patients who had undergone forehead rejuvenation over the previous 10 years asking them whether they had experienced MH prior to the surgery and if they noticed any change in their MH and in what way.

Conflicts of Interest: None.

Results of the Retrospective Study

Of the 249 patients who responded to the questionnaire, 39 confirmed having MH prior to the surgery and 31 ($P<.0001$) had observed either complete elimination or significant improvement (at least 50% reduction) of their MH.[23] Of note was the consistency of the incidence of MH in this surgical group, which closely matched what is noted in the general population (12%).

Discussion on the Retrospective Study

This was a retrospective study, thus it was dependent on the patients who responded and on patient recall. It did confirm, however, that the observation made by the patients was not mere coincidence. This study also offered compelling evidence against the placebo effect being the reason for the improvement or elimination of MH after surgery as these patients did not undergo surgery for treatment of MH nor were they aware of such a connection between their surgeries and MHs; therefore, they were not anticipating any change in their MH as a result of the forehead surgery.

Migraine Headaches Changes Following Injection of OnabotulinumtoxinA

Coinciding with the reports that forehead surgery was resulting in MH improvement or elimination, patients once more made the observation that their MH stopped or improved after receiving onabotulinumtoxinA (onabot) injection for cosmetic reasons.[27] It occurred to us that the only possible logical common ground between these two totally disparate observations was ablation of the muscle contraction potentially irritating the nerve, one reduced through surgery and the other through chemical denervation.

We have more information on the possible effect of onabot on sensory neurons. Interestingly, the efficacy of onabot was also considered a placebo effect by the same adamant skeptics[1,28] who now use this modality for prevention of chronic MHs after multicenter studies demonstrated its effectiveness.[29]

PROSPECTIVE PILOT STUDY

Encouraged but not totally convinced with the findings from our retrospective study and reports of onabot effects on MH, it seemed logical to test the hypothesis that decompression of the peripheral trigger sites might help migraine patients. Therefore, we designed a prospective pilot study.

Methods for the Prospective Pilot Study

In this prospective pilot study our research team, including Dr. Tarvez Tucker, a neurologist specializing in headaches from the Department of Neurology at Case Western Reserve University at the time, designed a prospective pilot study. Onabot was injected first to emulate the effects of surgery by paralyzing the muscles, not as a therapeutic measure as stated by Professor Diener and Dr. Paul Mathew.[30] Only those who responded favorably to the injection of onabot underwent surgery, as the main purpose of the surgery was to eliminate the muscle function and if onabot failed to produce positive results, it meant to the research team that the surgery would not be likely to be beneficial to those patients.

Results of the Prospective Pilot Study

Of the 22 patients diagnosed and selected by the neurologist to have MH based on the International Headache Society (IHS) classification who underwent surgery, 21 noted a positive change in MHs: 10 experienced elimination and 11 reported significant improvement (at least 50% reduction in severity, frequency and duration of MH) ($P<.001$) over approximately a year of follow-up.[22]

Discussion on the Prospective Pilot Study

While the results of the pilot study were very promising, it was puzzling to us that not all of the patients experienced elimination. Listening to these patients carefully, however, it became clear that in reality many of them observed elimination of MHs localized to the targeted decompression sites. However, some continued to have MHs localized to sites other than where the nerve was decompressed. This led us to realize that MH can be triggered from different anatomical sites and we needed to learn about all of the potential sites to be able to help the patients more successfully.

We next reviewed the anatomy of the pericranial nerves that were potential MH trigger sites beyond the forehead and temple areas to identify other compression sites. Careful assessment of the patients who partially benefitted from the surgery in our pilot study indicated that the remaining MHs were mostly located in the occipital region; some patients had pain in the retrobulbar area. Our anatomical studies on 20 fresh cadavers demonstrated that the greater occipital nerve passed through the semispinalis capitis muscle to reach the skin level in all 40 dissected sides.[18] We designed a surgical technique to decompress this nerve with the hypothesis that the nerve is being irritated or compressed by the contraction of the muscle encasing the nerve.

We also noted some patients reporting elimination of MH following septoplasty and turbinectomy, which led us to believe that there was another trigger site inside the nose and the nasal septum area. A literature search uncovered a previous article that had reported cessation or improvement of MHs after septoplasty and turbinectomy.[31]

A COMPREHENSIVE STUDY

Armed with multiple pieces of crucial information from patient reports, injection of onabot as a predictor for positive clinical response to the surgical removal of muscles, and utilizing anatomical knowledge and clinical studies, we designed a

more comprehensive study to include all potential trigger sites known to us at that time.[16]

Methods for the Comprehensive Study

Volunteers who had failed to benefit from the preventative and abortive treatments were enrolled in the study. As with the previous study and all of the subsequent clinical prospective investigations, the neurologist of the research team, Dr. Jennifer Kriegler, a headache specialist from Case Western Reserve University who is currently at the Cleveland Clinic Headache Center, examined the patients and made a diagnosis of MH based on the IHS classification. Dr. Kriegler excluded other conditions that could mimic MH or those patients with medication overuse headache (MOH).

One hundred twenty-five patients were enrolled in this study, with 25 serving in the control group and 100 in the treatment group. The number of subjects assigned to these groups and their randomization were planned by the experienced biostatistician of the research team.

Validated headache study tools including the Migraine-Specific Quality-of-Life Questionnaire (MSQ), Migraine Disability Assessment Scale (MIDAS), and Short Form (36) Health Survey (SF-36) questionnaires were completed by the patients before surgery and 1 year after surgery. None of the patients in the treatment and control groups had their maintenance medications altered during the follow-up period, except for those who experienced elimination of their MH. The preventive medications were discontinued for these patients who no longer needed them. The study nurse coordinator collected the patient data in a password-controlled database, and the surgical team had no access to this information at any point. The data were delivered to the biostatistician directly by the nurse coordinator. The data were analyzed by the biostatistician, and the results section of the article was written and the tables and graphs were prepared by the biostatistician without the involvement of the surgical team.

Results of the Comprehensive Study

Ninety-eight of the patients in the treatment group received injection of onabot in the trigger sites to match the surgical effect by paralyzing the target muscles and to avoid surgery on patients who may not benefit from the removal of the muscles. Of these, 91 responded to the injection of onabot and underwent surgery and 89 completed the 1-year follow-up. Out of the 25 patients in the control group, 19 completed the 1-year follow-up.

The adverse events were carefully elicited and documented on every patient and most were transient or easily treatable. There were no serious or lasting complications. None of these patients reported deterioration of MH after the surgery. Eighty-two of 89 (92%) patients in the treatment group observed at least a 50% improvement in the frequency, intensity, and duration of MH ($P<.00001$), of which 31 (35%) noted complete elimination and 51 (57%) experienced significant improvement. None of the patients in the control group reported elimination, and only 3 (16%) patients reported improvement greater than 50%. All 10 of the measurable parameters in the headache study tools (MSQ, MIDAS, SF-36) demonstrated significant positive changes in the treatment group compared to their baseline values as well as the control group ($P<.001$). The loss of work time was reduced from 4 days/month to 1 day/month.

Discussion on the Comprehensive Study

When the results of the surgery within the first 3 postoperative months were compared to the subsequent 3 quarters, there was a steady, statistically significant pattern of improvement in the results in each quarter. This improvement most likely was the consequence of healing and provides another piece of evidence against the placebo effect where one would have expected the opposite pattern.

5-YEAR FOLLOW-UP

Methods for the 5-Year Follow-Up

In a 5-year follow-up arm of the above study,[13] patients were examined by the research team and were asked to complete the MH log, the SF-36, MSQ, and MIDAS questionnaires that they had completed previously, at a minimum of 60 months after surgery. The neurologist and the surgical team were able to follow 79 patients for 5 years. Again, the data were collected by the study nurse coordinator under the scrutiny of the IRB and analyzed by the biostatistician without any involvement of the surgical team. The results section of the article was written solely by the biostatistician, and he prepared the tables and graphs. Ten patients, who had observed significant improvement but not elimination, underwent deactivation of additional (different) trigger sites during the 5-year follow-up period in an attempt to eliminate their headaches, and these patients were not included in the final data analysis. However, the overall outcome with or without inclusion of these 10 patients was analyzed, and there was no statistically significant difference.

Results of the 5-Year Follow-Up

Sixty-one of 69 (88%) patients continued to have a positive response to the surgery after 5 years ($P<.0001$). Twenty (29%) reported complete elimination of MH, 41 (59%) noticed a significant decrease in frequency, severity, and duration of MH, and 8 (11%) observed no significant change ($P<.0001$). All of these end points were assessed independently, as clearly demonstrated in the tables and text of the published article. When compared to the baseline values, all 10 measured variables including MIDAS, MSQ, and SF-36 improved significantly at 60 months ($P<.0001$). Based on the 5-year follow-up data, there is strong evidence that surgical

decompression of one or more migraine trigger sites can successfully cease or diminish the MH frequency, duration, and intensity in a lasting manner.

Discussion of the 5-Year Follow-Up

Ten patients were lost during the 5-year follow-up. A suggestion has been made that these were the patients who had complications or poor outcomes and that is why they were not included in the analysis. The study nurse coordinator vigorously pursued these patients to schedule a follow-up but she was not able to reach them via phone or mail. Those who failed the surgery or observed complications were entitled to have continued care, including preventive and abortive medications without incurring any costs. Had these 10 patients experienced failure to improve or deterioration, one would hypothesize that they would have been eager to receive uncompensated care. A more likely scenario is that these patients did not need any care and did not want to complete the three cumbersome questionnaires. This hypothesis has not been promulgated before and is offered merely as a counterpoint for those who wish to have balanced assumptions. However, our conclusions are based on facts, and we assume these subjects were lost during the follow-up period. We consider any conjecture of a positive or negative contribution from these 10 patients to the final outcome of the study inappropriate. Likewise, the supposition of an 88% placebo effect lasting 5 years, as claimed by Professor Diener, we believe to be totally unsound.

A RANDOMIZED STUDY WITH SHAM SURGERY

To obtain the ultimate evidence of the efficacy of surgical decompression of MH trigger site, we planned a study with a sham surgery arm with enormous inherent challenges. Studies including sham surgery are extremely unusual due to the difficulty in securing an IRB approval and the complexity of proper study.

Methods for the Randomized Sham Surgery Study

After obtaining IRB approval from 2 separate boards, patients with a single trigger site or MH predominantly localized to one site were recruited and randomized to receive placebo surgery or real surgery.[14] This study required interviewing 315 patients, as MH patients rarely have a single trigger site or one predominant trigger site. Also, due to the fact that septoplasty and turbinectomy are done through the nostrils with no visible incisions, and thus the placebo effect could not be produced, patients with nasal trigger sites were excluded. The two research team neurologists, including Dr. Jennifer Kriegler and another board certified and fellowship trained headache specialist, Dr. Deborah Reed, selected the patients. The number of subjects assigned to the real surgery and sham surgery groups, as well as their randomization technique into the groups, was decided by a highly respected and experienced biostatistician. Because of the nature of the study (inclusion of sham surgery), the biostatistician assigned the minimum number of patients in the sham surgery and the treatment groups that would provide sufficient statistical power. The patients underwent injection of onabot to simulate the surgery effect by paralyzing the muscle. The sham surgery patients underwent the incision, the nerves and muscles were identified, but the muscles were not touched, and the nerves were not decompressed.

All data were collected and stored by the study nurse coordinator without any input from the surgical team and delivered directly to the biostatistician of the team. The study nurse coordinator was blinded to the nature of the surgery. The data were analyzed and the results section of the article was written by the biostatistician who also prepared the tables and graphs without any input from the surgical team. The neurologists discontinued the preventive medications for those who experienced elimination of MH; otherwise, the medications were not changed.

Results from the Randomized Sham Surgery Study

Seventy-five of 76 patients enrolled in the study completed the 1-year follow-up. Forty-nine of those patients served in the treatment group, and 26 were assigned to the sham surgery group. Forty-one of the 49 (83%) patients benefitted from the real surgery compared to 15 of 26 (56%) patients in the sham surgery group ($P = 0.014$). While 28 (57%) patients in the real surgery group observed complete elimination, only 1 patient in the sham surgery group reported elimination ($P < .0001$). The real surgery group had significant improvement in all of the validated MH measurements (MSQ, MIDAS, SF-36) at 1 year ($P < .01$) compared to the sham surgery group. The adverse effects were carefully recorded, and most were transient. The adverse effects, which persisted after 1 year, included forehead numbness in one patient, residual corrugator muscle function in one patient, and neck stiffness in another patient.[14]

Discussion of the Randomized Sham Surgery Study

It was once more concluded that surgical treatment of MH is efficacious and safe through this highly unusual and demanding study.

ELECTRON MICROSCOPIC AND PROTEOMIC ANALYSIS

In a more recent study, the nerves of patients who had MH were compared to those without MH to investigate whether there were any structural differences.

Methods for the Electron Microscopic and Proteomic Analysis

Following IRB approval, a segment of the zygomaticotemporal branch of the trigeminal nerve was removed in 15 patients who experienced MH, diagnosed by the neurologist

of the team. These nerve segments were compared using proteomic analysis and electron microscopy to the nerves of 15 volunteer patients who never had MH but were undergoing forehead rejuvenation plastic surgery. Two independent departments at Case Western Reserve University (Center for Proteomics and Bioinformatics and Department of Neurosciences) analyzed their study results and the researchers wrote the respective results sections from each department independently.

Results of the Proteomic Analysis and Electron Microscopy

Proteomic analysis identified differentially expressed proteins and networks composed of highly connected molecular modules (P values of 10^{-44} and 10^{-34}) on patients with MH. The nerves from patients with MH had a linear organization, disrupted myelin sheaths and target axons, and discontinuous neurofilaments that were poorly registered with the discontinuous myelin sheaths, suggesting axonal pathology.

Discussion of the Proteomic Analysis and Electron Microscopy

This study was presented as a poster during the IHS annual meeting in June 2013 and has been published.[32] The implications of this study are that patients who suffer from MH may have myelin deficiency, and vulnerable nerves could be readily irritated peripherally and thus begin the cascade of events that ultimately results in the full MH complex. This study reinforces the role of peripheral mechanisms in MH and provides a probable explanation as to why surgery and onabot may work, without diminishing the important role of central mechanisms.

CURRENT PRACTICE

Our studies have demonstrated that there are 4 common headache trigger sites, including the frontal, temporal, occipital, and rhinogenic sites. There are additional, less common trigger sites such as the auriculotemporal, lesser occipital, and some minor terminal branch sites. The key to the detection of the trigger site is knowledge of the constellation of symptoms, and the most important one is the site from which the headaches appear to originate. Almost all patients can readily identify the site where their headaches arise. Some may require probing to elicit this crucial piece of information. Our team requires the patients to maintain a log of their MH for one month prior to their first visit with our team. The additional pieces of information in the log are independent sites from which the headaches start, frequency, duration, intensity, associated symptoms in detail, and the triggers of MHs.

We have learned that in the frontal area, most of the headaches appear to start from the supraorbital region. These patients commonly have a strong corrugator muscle group with deep frown lines and may develop eyelid ptosis at the time of their headaches. One can produce tenderness at or immediately above the eyebrows by gentle pressure. Patients in which supratrochlear and supraorbital arteries irritate the nerve, compressing the painful site firmly enough to stop the blood flow, may temporarily abort the pain in the early stage of the migraine cascade. The involved nerves in the forehead include the supraorbital and supratrochlear nerves that pass through the corrugator supercilii muscle group, including the corrugator supercilii, depressor supercilii, and medial fibers of the procerus muscles, to reach the skin level.

On patients who identify the mid or upper forehead headache headache trigger site with a fingertip one may detect an ultrasound Doppler signal in the most tender site. This site often coincides with the course of supraorbital or supratrochlear nerves and related artery branches. A computerized tomography (CT) scan of the paranasal sinuses on these patients may reveal the presence of a supraorbital foramen through which the supraorbital nerve passes to innervate the forehead skin. The foramen, while it may not be the location of the MH trigger, can confine the inflamed supraorbital nerve and accompanying vessels to a narrow tunnel, thus intensifying the pain. It could be debatable whether the inflammation/irritation of the nerve is part of the migraine pathophysiology (through release of neurotransmitters) or another primary pathology that triggers the headache phase of MH, and this will need to be investigated. However, the future findings will not change the fact that decompressing this inflamed nerve in the patient who has the diagnosis of MH will reduce or stop the headaches.

Temporal MHs commonly begin from a point approximately 17 mm lateral and 6 mm cephalad to the lateral canthus, the center of which is a hollowed area that is easily detectable by palpation. This is the site where individuals with or without MH may rub when they feel tension or sense the beginning of a headache. The patients with temporal MH have a common history of clenching their jaws and grinding their teeth, and may wake up with pain in this site. They often use a bite guard with variable success. The main nerve involved in this site is the zygomaticotemporal branch of the trigeminal nerve that passes through a bony foramen in the lateral orbital wall and the deep temporal fascia to reach the skin level. In a small percentage of patients with MH (5%), the auriculotemporal branch of the trigeminal nerve or its terminal branches are involved. This nerve could be irritated by the surrounding branches of the superficial temporal artery.[7] The pain in this group of patients will be felt closer to the ear, immediately above the helix or sometimes close to the temple hairline. One can commonly detect an ultrasound Doppler signal in the center of the most intense pain site. Patients can often identify this center of the pain precisely by some probing and by asking them to point to the pain site.

New daily persistent headache may commonly involve this site.

Patients with rhinogenic MH commonly complain of pain that starts in the retrobulbar region. The patients are often awakened with headaches in the middle of the night or in the morning. Low atmospheric pressure, hormonal changes, and recumbent position, can all result in engorgement of the turbinates and more intense contact, thus triggering MH. Many of these patients have all of the associated symptoms that place the headaches in the MH class based on the IHS classification. The headaches in this group of patients are often unresponsive to onabot injection, or the response is just improvement rather than elimination. High atmospheric pressure, use of nasal oxygen, spraying vasoconstrictive agents, and an erect position can reduce the MH for these patients. These are the patients who are usually misdiagnosed as having sinus headaches and receive antibiotics on a regular basis.

The paranasal CT scan on these patients is often very informative. Commonly, there are multiple contact points involving spurs and concha bullosa. Haller's cell or paradoxical curl of the turbinates can also be seen on the CT scan. The paradoxical curl in the turbinates may result in misdirecting the air toward the septum horizontally, which can irritate the nasal lining, triggering MHs. In addition to the improvement in their MHs, the majority of these patients can breathe more comfortably through the nose postoperatively, a side benefit of the operation.

Occipital MH often begins where the greater occipital nerve exits from the semispinalis capitis muscle, which is usually 35 mm caudal-lateral to the occipital protuberance and 15 mm lateral to the midline.[18] One can cause tenderness by gentle pressure where the nerve exits from the muscle, and the muscles are often tight. Many of these patients have a history of whiplash injury. Occipital nerve compression can also be associated with retro-orbital referred pain. An occipital nerve block may help distinguish occipital from rhinogenic referred retro-orbital pain.

Some may argue that this irritation of the occipital nerve is not due to MH, and that it is a separate pathology, such as occipital neuralgia. However, these patients' headaches often fulfill the criteria for MH when evaluated by our neurologists. More importantly, these patients often respond to the decompression of the nerve, and from the patients' point of view, the diagnosis is irrelevant.

The lesser occipital nerve irritation causes pain in the lateral portion of the occipital region, at the hairline or immediately below the hairline, extending to behind the ear and the temple area.

SURGICAL CORRECTION

The surgical procedure in the frontal region involves removal of the unwanted frowning muscles, elimination of which, even though it is incomplete, results in pleasing changes in the glabellar region in addition to improvement or elimination of MH. Foraminotomy, removal of the supraorbital and supratrochlear arteries, and fasciotomy are done as adjunct procedures if indicated by the symptomatology and pathology. We are currently conducting a randomized study to define the importance of each of these elements in reducing or eliminating frontal MHs.

Supraorbital and supratrochlear nerves are commonly decompressed through an incision in the upper eyelid crease if there are no concomitant temporal MHs. This is a technique that was devised for elimination of the frown lines by our team in 1993 for cosmetic purposes, and it is now a routine plastic surgery procedure for its initial cosmetic purpose,[33] as well as surgical decompression of frontal migraine trigger sites. However, the surgery will be performed endoscopically if the MHs start from both the frontal and the temporal sites independently. The frontal procedure is always performed bilaterally to maintain symmetry. The transpalpebral approach requires 45 minutes, and the combined frontal and temporal surgery consumes 75 minutes.

In the temporal region, the current routine procedure is either decompression of the nerve by enlarging the fascia opening or removal of a segment of the zygomaticotemporal branch of the trigeminal nerve. This procedure can be performed unilaterally. This nerve has been transected by plastic surgeons and neurosurgeons for decades for a variety of reasons including cosmetic as well as craniofacial, and intracranial surgeries that require elevation of a temporal flap. There are no reports of neuromas related to transection or removal of this nerve in the literature. This may have to do with the fact that nerve retracts in the muscle and the transected or avulsed nerves that are buried in the muscle will have the lowest incidence of neuroma. However, we recently completed a randomized study in which we resected the nerve on one side and decompressed the nerve on the other side in patients with bilateral temporal MH to compare the outcome. Our results demonstrated no significant difference in the outcomes between the two procedures.

The auriculotemporal trigger sites can often be deactivated by removing the adjacent vessel and decompressing the main nerve or its branches under local anesthesia in less than 15 minutes without any associated recovery. This means that the patients can return to work the same day or the next day.

For rhinogenic MH, the contact points are eliminated by straightening the deviated septum, removing the spurs, reducing the size of the turbinates, eliminating the concha bullosa, or various combinations of these techniques. This surgery usually takes about 20–30 minutes.

In the occipital area, a small segment of the semispinalis capitis muscle is removed medial to the nerve and replaced with a subcutaneous soft tissue flap to shield the nerve.

Additionally, the nerve is decompressed by removing the fascia bands and the vessel wrapped around the nerve and the nerve is followed to the subcutaneous plane. This surgery takes approximately 75 minutes for a bilateral procedure. The lesser occipital nerve also is commonly irritated by the adjacent vessel, which would be removed and the nerve decompressed under local or general anesthesia. This is another site where ultrasound Doppler plays a major role in precise detection of the offending vessel and locating the nerve without too much dissection.

All surgical procedures are performed in an outpatient surgery center unless the patient's medical condition or excess weight mandates an inpatient surgery due to the potential for sleep apnea and the need for observation. The patients resume routine activities in a few days and strenuous activities or exercises in 2–3 weeks, depending on the site of surgery.

The risks of surgery including infection, bleeding, persistent numbness, injury to the frontal branch of the facial nerve, dryness of the nose, persistent MH, and deterioration of the pain are discussed with the patients. Every patient experiences some numbness, but permanent numbness and the above complications are exceedingly rare, as demonstrated in our studies. For a lengthier procedure, one has to include the possibility of thromboembolism, which is the rarest of complications, and we have not observed this complication after over 1000 patients undergoing 2600 migraine decompression surgeries. Rarely, patients may experience intense itching in the forehead, which may often respond to topical lidocaine (4%) or antihistamines. There are a few patients who report deterioration of their symptoms postoperatively, and we are currently studying the factors that could be governing this type of outcome. Overall, in experienced hands, these procedures are highly successful and safe.

PATIENT EVALUATION

Our group has never operated on a patient without preoperative examination by a neurologist. Almost all of our patients have been treated by multiple neurologists using a variety of preventive and abortive treatments prior to their visit with us. Many patients have a failed nerve stimulator that is still in place or has been removed for a variety of reasons, including infection or failure of the device. While we routinely used onabot for the detection of the trigger sites in the beginning stages development of migraine surgery, we have come to the conclusion through evidence-based information that injection of onabot is not always necessary, and we can produce similar outcomes using a combination of a constellation of symptoms and a CT scan of the paranasal sinuses, when indicated, for detection of the trigger sites.[11] The algorithm for onabot injections was designed to guide the inexperienced surgeon to identify the trigger sites. Failure of response to onabot injections in the occipital area often means that the patient may have occipital neuralgia, which usually responds very favorably to the nerve decompression, as indicated earlier. While patients with nasal, septum, or sinus related trigger sites commonly do not respond to the onabot injections as favorably, some secondary pain due to the spread of inflammation in the peripheral branches of the trigeminal nerve can be abated by injection of onabot. This injection will reduce the added insult induced by contraction of the frontal and temporal muscles or through direct effect of the onabot on the sensory nerves. However, the basic retrobulbar MHs, thus the frequency, will often remain unchanged for this group of patients.

The dose of onabot injections in the assessment of the patients for surgical treatment is totally different from that which is used therapeutically by our neurology colleagues for prevention of chronic migraine. Generally, we inject 25U in the glabellar muscle group (12.5U/side), 25U in each temporalis muscle, and 25U in each semispinalis capitis muscle. Essentially, we are achieving similar results to onabot injections with surgery, but in a more lasting manner. The surgery for MHs is not dissimilar to decompression of nerves during carpal tunnel surgery, which is accepted by most of our neurology colleagues. Currently, the majority of the insurance carriers reimburse our team for the services that we provide.

DISCUSSION OF THE DEBATE

Professor Diener began the IHS scientific meeting debate in 2013 by showing a disclosure slide that connected him with 30 commercial entities and admitted that he has a bias. He took a strong position against the surgery. He then showed the home page of a website in which he stated that I claim that I cure MHs, which is not accurate. The website that he showed belongs to the American Migraine Center where we have 2 full time headache specialists, and the website refers to a variety of headache treatments offered within that center. The assertion was not exclusively about the surgical treatment of MHs and only a very small percentage of the patients who are treated in this center are referred to have surgical decompression of MH trigger sites.

Professor Diener announced that he stopped the German insurance companies from paying for migraine surgery. This could harm the patients who are desperate, because the small group of patients who are not the beneficiary of his treatments and are in enough pain to need a solution will have to pay out of pocket in Germany, or worse, travel to the USA so that our team and others can help them.

Professor Diener then questioned why 317 patients were screened in our sham surgery study, and only 130 received

onabot injections. As I indicated above, the neurologists of the team were looking for patients who had a single trigger site or predominantly single trigger site, which is not common. They also excluded patients who had a nasal trigger site, as these patients do not have a visible incision and a placebo effect could not be anticipated.

He unfairly declared that the patient selection was not described in the article. It is clearly stated in the articles that the neurology board certified, headache specialists of the research team using the IHS criteria selected the patients. Professor Diener also stated that prior treatments and medications as well as history of depression were not listed. We believed simply stating that the selection was done by a qualified neurologist using the IHS criteria was sufficient to conclude that the diagnosis was correct and MOH was ruled out. A history of depression was not part of the exclusion criteria because the co-morbidity of migraine and depression is high. It would have excluded many patients who could have benefitted from surgery for their chronic intractable MHs.

A remark has been made that the patients should have been followed by an independent examiner after surgery. We felt that this was unrealistic in a 5-year study, it is not something routinely done in the surgery field, and it did not occur to us. We respect our colleagues who have devoted a portion of their lives to research, often on the weekends and evenings, to help serve patients better. Research of this type is a team effort, and as indicated in the abstract, there were 27 members involved in the different stages of the research projects that we have completed.

Professor Diener also suggested that I am attempting to discredit the trigeminovascular theory of MH. There is no such statement anywhere in our reports. Even though I have advocated the role of peripheral mechanisms based on our findings, the efficacy of surgical procedures and onabot injections, I have never dismissed any other theories as I am not qualified to define the complex MH pathophysiology.

Professor Diener questioned the use of onabot during the selection process. What Professor Diener seems to have misunderstood is that the role of the onabot was not therapeutic or preventive. As noted above, we injected onabot to emulate the surgical removal of the muscle by chemically paralyzing the muscle to test the beneficial effects of eliminating the muscle function on the potential surgical candidates. The surgeries were performed at least 3 months after the last onabot injections, and more importantly, after assuring that the muscle function recovered completely and the MHs returned.

Professor Diener stated that our randomization of 2:1 resulted in less statistical power and an increased placebo effect. As was explained earlier, the number of subjects was determined by a highly respected and experienced biostatistician. There is considerable complexity involved in the design and conduct of a study that includes sham surgery. Subjecting more patients to a sham surgery than what is absolutely necessary is unjustified. The sufficient statistical difference between the sham surgery and treatment groups in our study should have been convincing.

Another criticism brought up by Professor Diener was that the blinding in our study was not sufficient. Surgery in the forehead area is the only part that could be open to question. It is important to understand that all patients maintain some movement in the glabellar muscles after the surgery due to incomplete removal of the corrugator supercilii muscle, in spite of concerted efforts. Additionally, only a minimal amount of the medial fibers of the procerus muscle are removed by design, and the function of the frontalis and orbicularis oculi muscles are retained fully. Collectively, these intact muscles create enough movement in the forehead area for the patient to not be able to clearly judge whether the corrugator muscle was removed or not. This is radically different from the FDA-approved protocol of onabot injections for chronic migraine, where the forehead is essentially frozen. In fact, the muscle function in the forehead in our studies was significantly more than what was described in the EU Phase 3 onabot randomized controlled study.[29] Conversely, patients who undergo sham surgery have some reduction in the muscle function temporarily due to the surgery and swelling. Additionally, patients were hoping for elimination of MH and, had the placebo effect been a strong factor, one should have observed more elimination in the sham surgery group rather than improvement. The fact that only one patient (4%) in the sham surgery group reported elimination of MH compared to 28 (57%) in the treatment group ($P<.0001$) was another strong piece of evidence that the placebo effect was not the reason for the positive changes.

The Migraine Index, which we used, was not the only endpoint in our studies. We also included 50% reduction in frequency, severity, and duration as independent endpoints. We believe the Migraine Index captures all of the variables, but again, it is not the only value we rely on. Migraine-days as a measure of success misses the intensity change, which is more crucial for most patients. Many patients are happy to have less intense MHs, which allows them to carry on their daily function, while the frequency and duration may not change. Migraine-days would overlook this life-altering change. Additionally, our studies began well before the Phase 3 onabot registration studies. Outcome measures for intervention were hotly contested for those studies as well. We needed to create a method of measurement that would have a longitudinal interstudy reliability throughout our 14 years of research. While other measures now exist, we have adhered to some measures to enable us to evaluate differences between our studies and account for any changes in outcome our treatment paradigms may have created. This was part of the

motivation for our current technique-related studies that are in press. And, as noted above, we also used MIDAS, MSQ, and SF-36, all of which have demonstrated statistically significant improvement in surgical patients.

Both the neurologist and the surgical team followed these patients post-operatively. The surgical team never prescribed any migraine medications. Even those who did not need medications visited the neurologists.

Professor Diener argued that as no previous study has shown over 5% cure, our numbers could not be correct, and that this must be a placebo effect. The fact that there was no more than 5% cure rate in the past does not mean that there will never be a more successful procedure to stop and or reduce MHs. This actually is the cardinal reason that the patients are so desperate to find a better solution for themselves. In reality, any surgical results with less than an 80–90% success rate would not be acceptable for most surgeons. While the patients are delighted to regain a minimum of 50% control of their lives 90% of the time, this is not completely satisfying to our team. We are striving for higher elimination rates. We have full faith in our success rate and so do the over 1000 patients whom our team has treated surgically.

I question whether onabot or any other approved migraine preventive treatments change the epigenetics of migraine. Many genetic conditions can be improved or eliminated by surgery, including mastectomy on a patient who is genetically destined to develop breast cancer.

I would like to summarize my responses to the two main objections that Professor Diener brought up related to our studies.

Summary

Placebo Effect

A. It was the patients who first observed and reported improvements in their MH after cosmetic surgery. How could this be a placebo effect if neither the patients nor the surgeon was anticipating such an outcome?
B. Our first retrospective study surveyed the patients without disclosing what the intentions of the survey were. The patients were simply asked whether they had MHs prior to and after the forehead surgery. How could the results of this study be a placebo effect?
C. There are no scientific articles reporting an 80–90% placebo effect. Claiming that an 88% response rate that lasted 5 years is the result of a placebo effect is not scientific.
D. When comparing the results of the first quarter of the postoperative period to the subsequent quarters in our comprehensive study,[16] there was a steady and statistically significant improvement in the results, which is contrary to what one would expect from a placebo effect, where the initial higher success rate should decline over time.

Study Flaws

We used a team of qualified and highly experienced researchers including 3 respected, board certified neurologists specializing in headaches. We used a respected biostatistician with an international reputation for integrity with extensive experience and several hundred peer reviewed publications in reputable journals, 5 text books and over 40 book chapters to design and complete these studies. The neurologists selected the patients prior to the surgery and those with potential MOH or other conditions were excluded from the study. Both the neurologist and the surgical team followed the patients. Onabot was used in the selection process only for identification of the trigger sites by paralyzing the target muscle to assure surgical effectiveness, and not at therapeutic doses. Statistical comparison demonstrated matching treatment and control group demographics. The data were collected and stored by a study nurse coordinator and the data were directly delivered by the study nurse coordinator to the biostatistician without involvement of the surgical team. The biostatistician analyzed and wrote the results section of the articles and designed the graphs and tables without any input from the surgical team. Blinding was complete in the temporal and occipital sites and was adequate in the frontal region as no matter how hard one tries, complete elimination of muscle function, and thus forehead movement, with the surgery is impossible. Additionally, the frontalis and orbicularis oculi muscle function were never altered by surgery and, therefore, the forehead was not frozen the way it occurs with onabot. At the same time, the sham surgery often resulted in some swelling and reduction in the muscle function temporarily, which was enough to temporarily give an impression of muscle removal to the patients who had no muscle removed.

Patients can only benefit from collaboration between neurologists and plastic surgeons, as has been demonstrated by our team. We need to focus our collective energy in defining the correct terms, choosing the right patients, and helping those who are not served with the available preventive and abortive measures, which would only be a small percentage of the patients with MHs. Our neurology colleagues can better control the abuse of the surgical procedures by having an

open mind about surgery and referring this group of patients to those who are properly trained to deliver a more successful outcome. I strongly suggest that we start a dialogue, and form an alliance and a joint task force for the benefit of the patients. This way we can control the destiny more favorably.

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