Therapeutic Role of Fat Injection in the Treatment of Recalcitrant Migraine Headaches

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Background: This study was designed to assess the safety and efficacy of site-specific fat injection for the treatment of refractory migraine headaches following medical or surgical treatment.
Methods: A prospective cohort study was performed on consecutive patients who had migraine headaches with persistent symptoms after surgical decompression and were given therapeutic fat injections from September of 2012 to January of 2015 with 12 months' minimum follow-up. Clinical outcomes assessment included migraine frequency, intensity, duration, migraine headache index, and complications. A 50 percent or greater decrease in frequency, intensity, or duration was considered therapeutic success, whereas 10 percent or greater increase in migraine headache index was considered worsening of symptoms. Pairwise *t* tests were used to assess statistical significance ($p < 0.05$).
Results: Twenty-nine patients met inclusion criteria. All were female, with a mean age of 49.0 years (range, 21.5 to 72.5 years), and mean follow-up was 29.4 months (range, 12.3 to 49.5 months). Twenty patients (69.0 percent) experienced successful improvement; 12 (41.4 percent) experienced complete resolution. Five patients (17.2 percent) experienced subtherapeutic improvement, and four (13.8 percent) experienced worsening of symptoms. Mean improvement per patient at their last follow-up was 5.1 (39.3 percent) fewer attacks per month ($p = 0.035$); 3.1 (42.0 percent) lower intensity on a scale of 1 to 10 ($p = 0.001$); 31.8 (74.4 percent) fewer hours of duration ($p = 0.219$); and 52.8 percent lower migraine headache index ($p = 0.012$). There were no complications for any patient.
Conclusions: Migraine headache symptoms were successfully reduced in the majority of cases with fat injection. A comprehensive surgical treatment algorithm including this novel procedure is presented. (*Plast. Reconstr. Surg.* 143: 877, 2019.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

The prevalence of migraine headaches in the United States is 11.7 percent, or approximately 30 million people, affecting mostly women (17.1 percent of women compared to 5.6 percent of men).[1–4] Migraine headaches also affect adolescents.[5,6] The annual cost of treatment and medications for migraine headaches in the United States is $13 to $17 billion, and the annual cost of work days lost (112 million days per year) is $14 billion.[7–9]

Approximately 10 million Americans suffer from medically refractory migraine headaches.[10] Patients who have migraine headaches with persistent symptoms after medical management or those who cannot tolerate the side effects of medical therapy are candidates for surgical decompression. The success rate of surgical decompression

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ranges from 79 to 90 percent.[11–21] Patients often consider surgery as a last resort, and those who do not experience significant improvement after surgery can be emotionally devastated. Factors associated with migraine surgery failure are younger age at migraine onset, intraoperative excessive bleeding, and two or fewer surgical sites.[22,23] Factors associated with migraine surgery success are surgery at a frontal or zygomaticotemporal site or at multiple migraine trigger sites.[22,23]

There are few currently reported alternatives for migraine headache patients with persistent symptoms after medical management and surgical decompression. These alternatives include repeated nerve decompression with or without corticosteroid injection, radiofrequency therapy, and peripheral nerve stimulators.[24–26] Based on a systematic review in 2014 that included a total of 1253 patients treated with nerve decompression, 184 patients treated with nerve stimulation, and 131 patients treated with radiofrequency therapy, nerve decompression provided the highest success rate (86 percent compared to 68 percent and 55 percent, respectively; all statistically significantly differences).[26] Implantable nerve stimulators also posed a 31.5 percent rate of complications requiring a return to the operating room, whereas nerve decompression surgery and radiofrequency therapy did not (0 percent rate of major complications).[26] Patients with recalcitrant migraine headaches who fail nerve decompression surgery would benefit from another relatively safe intervention that can provide them with additional relief.

Electron microscopy and proteomic evaluation of trigeminal nerve branches from migraine patients has shown disrupted myelin sheaths and target axons with discontinuous neurofilaments that are poorly registered with the myelin.[27] Fat-derived mesenchymal stem cells have been shown to repair myelin in patients with demyelination disorders.[28] It is well known that stem cells are present in prepared autologous fat,[27,28] and it has also been demonstrated that autologous fat grafting at the time of peripheral nerve repair can improve nerve regeneration.[29] It is therefore postulated that the stem cell content of prepared fat, over time, may likely be involved in the helpful repair of axons and myelin and reduce the final scar burden in nerves, thereby improving clinical outcomes. Therefore, it is possible that fat injection may also be a helpful adjunct in the surgical treatment of migraine headaches.

We designed a prospective study of patients with recalcitrant migraine headaches to offer them therapeutic fat injection and determine whether this new treatment can provide additional relief of their symptoms. We hypothesized that fat injection at migraine headache trigger sites would significantly reduce migraine headache symptoms in patients who have persistent symptoms after surgical decompression.

PATIENTS AND METHODS

Study Design

After institutional review board approval, a prospective cohort study was performed on all patients who had migraine headaches with persistent migraine headache symptoms after surgical decompression and were given therapeutic fat injections over a 29-month period starting in September of 2012 through January of 2015. Procedure details recorded included site(s) injected, date of injection procedure since last surgical decompression, and date of last follow-up visit since fat injection. Patients with less than 12-month follow-up were excluded. Site injections were recorded per patient by anatomical site (i.e., frontal, supraorbital, zygomaticotemporal, greater occipital, auriculotemporal, or lesser occipital), regardless of being bilateral or unilateral.

Clinical outcomes assessed included migraine headache frequency (per month), intensity (on a Likert pain scale ranging from 0 to 10), duration (in hours), migraine headache index (i.e., frequency × intensity × duration), and complications. A 50 percent or greater decrease in frequency, intensity, or duration was considered therapeutic success. A 10 percent or greater increase in migraine headache index was considered worsening of symptoms. Statistical tests were performed using GraphPad statistical software (GraphPad Software, Inc., La Jolla, Calif.). Preinjection and postinjection symptoms were compared using Wilcoxon signed rank tests with a two-tailed value of $p < 0.05$ to determine statistical significance.

Fat Injection Technique

Fat was aspirated from the abdomen or lateral thigh in each patient using a 2-mm-bore harvesting cannula attached to a 10-cc syringe. A total of 10 to 30 cc was harvested, depending on the number of sites intended for injection. The fat was then prepared and injected using the Coleman technique.[32] Using 1-cc syringes with a small bore 0.7- or 0.9-mm blunt cannula, the prepared fat was injected at the intended trigger site(s) using small aliquots over multiple passes in a fanning motion into the area around each nerve identified as a migraine trigger. The area of injection was based

on knowledge of the locations of the relevant trigeminal and cervical nerve branches using surface landmarks (blind technique)[13–15,33–49] and the location(s) to which the patient would point as a site of migraine headache pain. A more diffuse area of pain received a wider area of injection. Injection was performed subcutaneously, subfascially, and deep to the nerve, along the course of the nerve and generally within the area of pain indicated by the patient. For example, for patients with discrete temporal pain after avulsion of the zygomaticotemporal branch of the trigeminal nerve, fat injection is performed subcutaneously within the area of pain and into the temporalis muscle itself where the nerve likely retracted into. For patients with residual diffuse pain in the occipital area, fat was injected in the deep subcutaneous plane, along the course of the nerve and into the semispinalis muscle along the nerve pathway. For all areas, a fanning injection technique was used, and the total amount of fat injected was as follows:

- Site I: Supraorbital and supratrochlear nerves (frontal site): 1 cc of fat per affected side.
- Site II: Zygomaticotemporal nerve: 2 cc of fat per affected side.
- Site IV: Greater occipital nerve: 2.5 cc of fat per affected side.
- Site V: Auriculotemporal nerve: 2 cc of fat per affected side.
- Site VI: Lesser occipital nerve: 2 cc of fat per affected side.

RESULTS

Of 32 consecutive patients who were analyzed, 29 met inclusion criteria. All patients were female (100 percent), with a mean age of 49.0 years (range, 21.5 to 72.5 years) and a mean follow-up of 29.4 months (range, 12.3 to 49.5 months) since fat injection (Table 1). A total of 37 sites were injected, with a mean of 1.28 sites injected per patient. The sites injected (unilateral or bilateral) included 13 frontal (35.1 percent), one zygomaticotemporal (2.7 percent), 14 greater occipital (37.8 percent), eight auriculotemporal (21.6 percent), and one lesser occipital (2.7 percent) (Table 1). The minimum interval between primary surgical deactivation and subsequent fat injection in this study was 3.3 months, and the maximum interval was 107.3 months (mean, 26.0 months). There were no major complications for any patient at any site injected.

Twenty patients (69.0 percent) showed significant improvement in symptoms (at least 50 percent improvement in migraine headache frequency, intensity, or duration). Twelve patients (41.4 percent) experienced complete resolution of symptoms. Five patients (17.2 percent) showed less than 50 percent improvement in symptoms. Four patients (13.8 percent) experienced worsening of symptoms (≥10 percent increase in migraine headache index). Compared to preoperative symptoms, the mean response rates to fat injection per patient at the last follow-up were as follows: 5.1 (39.3 percent) fewer attacks per month ($p = 0.003$), 3.1 (42.0 percent) lower intensity on a Likert pain scale ranging from 0 to 10 ($p < 0.001$), 31.8 (74.4 percent) fewer hours of duration per migraine headache episode ($p = 0.002$), and 42.4 (52.8 percent) lower migraine headache index ($p = 0.003$) (Fig. 1 and Table 2).

DISCUSSION

This study describes a novel surgical procedure for the treatment of recalcitrant migraine headaches. In the senior author's practice (B.G.), the percentage of patients demonstrating significant improvement in migraine headache symptoms after surgical decompression is currently approximately 90 percent.[12–15] With fat injection, the success rate of surgical intervention is now increased to 97 percent. This is the first study to date that describes a surgical procedure other than repeated nerve decompression, nerve stimulator implantation, radiofrequency therapy, or neurectomy that significantly improves migraine headache symptoms. The results of this study support that fat injection is safer than nerve stimulators with similar efficacy

Table 1. Patient Demographics and Sites Injected

	Value (%)
No. of patients	
Female	29
Male	0
Age, yr	
Mean ± SD	49.0 ± 12.9
Range	21.5–72.5
Follow-up, mo	
Mean ± SD	29.4 ± 9.3
Range	12.3–49.5
Sites injected*	
Frontal	13 (35.1)
Zygomaticotemporal	1 (2.7)
Greater occipital	14 (37.8)
Auriculotemporal	8 (21.6)
Lesser occipital	1 (2.7)
Total	37

*Mean, 1.28 per patient (range, 1–2).

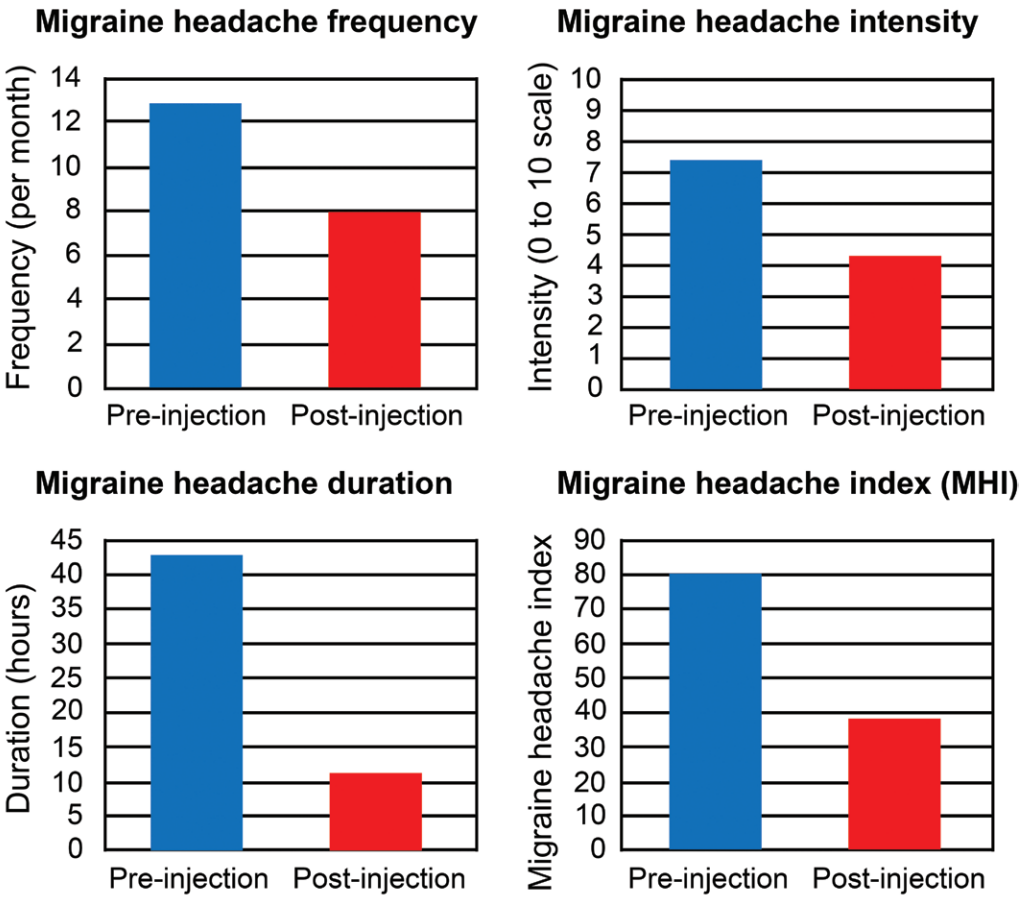

Fig. 1. Patient migraine headache symptoms before and after fat injection. Pre– and post–fat injection mean migraine headache symptoms are depicted in the four panels as follows: (*above*, *left*) frequency, (*above*, *left*) intensity, (*below*, *left*) duration, and (*below*, *right*) migraine headache index (*MHI*) (i.e., frequency × intensity × duration). Postinjection improvements in frequency, intensity, and migraine headache index were statistically significant ($p < 0.05$).

(0 percent risk of major complications versus 31.5 percent, 69 percent success versus 68 percent) and is more effective than radiofrequency therapy (69 percent versus 55 percent).[26] Thus, fat injection is the most reasonable alternative therapy for patients with migraine headaches that have failed medical management and surgical decompression.

Table 2. Patient Migraine Headache Symptoms before and after Fat Injection

	Before Injection*	After Injection*	Change (%)†	*p*
Frequency (per month)				0.003‡
Mean	12.9 ± 10.1	7.9 ± 10.7	−5.1 (−39.3)	
Range	1–32	0–30		
Intensity (on a 0–10 scale)				0.001‡
Mean	7.4 ± 1.9	4.3 ± 3.6	−3.1 (−42.0)	
Range	4–10	0–8.5		
Duration, hr				0.002‡
Mean	42.8 ± 131.2	11.0 ± 31.0	−31.8 (−74.4)	
Range	3.5–720	0–168		
MHI				0.003‡
Mean	80.3 ± 84.3	37.9 ± 75.4	−42.4 (−52.8)	
Range	3.4–300	0–318.5		

MHI, migraine headache index (i.e., frequency × intensity × duration).
*Mean ± SD and range.
†Mean change from before to after injection.
‡Statistically significant.

The initial surgical treatment for migraine headaches should still be thorough decompression of the affected nerves that involves myectomy, fasciectomy, supraorbital osteotomy, and arterectomy, where indicated. Neurectomy is occasionally performed as a last resort during revision surgery in patients with recalcitrant migraine headaches to achieve some improvement at the expense of numbness, which is often a welcome change for these patients.[13–15,50,51] The only instance where neurectomy is routinely performed at initial surgery is at site II (zygomaticotemporal).[51] Fat grafting is also performed at the time of primary decompression, such as free globular fat grafts from the temporal fat pad for site I or adipose flaps for site IV, which theoretically provide mechanical padding for the nerves and help minimize contour deformity after myectomy.[13,15] Now a closed procedure, fat injection may be used as an adjunctive therapy at a later treatment date for significant improvement, with no reported numbness in patients with recalcitrant migraine headaches. In the current study, fat injection was performed without ultrasound guidance, and zero instances of fat embolism were observed.

With surgical decompression, muscles and arteries may be excised to reduce pressure on the relevant nerve branches at each migraine headache trigger site. With fat injection, tissue is added instead of being removed. The exact mechanism of action for the therapeutic benefit in these patients is currently unknown. Similar to the observed benefits of fat grafting on peripheral nerve regeneration[30,31] and fat-derived stem cells on myelinization,[28] we believe that the stem cell content of the prepared fat, over time, is likely involved in the helpful repair of axons and myelin and in the reduction of the final scar burden for nerve branches in migraine patients, thereby resulting in less nerve irritation and subsequent migraine triggering. Although it is possible that physically breaking the continuity of scar and fascia with fat injections may play a role in symptom improvement, the number of passes with such a small-bore needle is not enough to create a meaningful release of scar/fascia. In contrast, the proposed role of fat-derived stem cells seems more plausible. Further study involving electron microscopy and proteomic evaluation of tissue samples is needed to confirm this theory.

A comprehensive algorithm for the surgical treatment of migraine headaches based on the senior author's practice is depicted in Figure 2, which now includes fat injections. Patients who have failed medical management (because of continued pain or intolerance of medication side effects), including botulinum toxin type A, or those refractory to botulinum toxin type A after a favorable initial response, are referred to a surgeon for primary trigger site analysis and surgical decompression.[52] The detection of trigger sites begins by assessment of the patient's constellation of symptoms and the site of pain onset for migraine headaches; patients are compelled to point with one finger to the area.[52] A positive response to botulinum toxin type A is a positive predictor of success after surgical decompression.[22] Targeted botulinum toxin type A treatment at a primary trigger site may also be used to determine whether secondary trigger sites exist.[52] No response to botulinum toxin type A treatment is not an indication that migraine surgery will not be helpful, as there are other structures such as arteries and bone that could cause compression but may not respond to the mechanism of action of botulinum toxin type A.[52] A nerve block during a migraine headache can be useful in identifying trigger sites but is not necessary.[52] A portable ultrasound Doppler probe can be used to identify any vessel signal that may be contributing to nerve irritation in the area.[52,53] Computed tomographic analysis is necessary for those with retrobulbar migraine headaches to identify intranasal contact points and concha bullosa.[23,52] Review of available computed tomographic data is also useful in patients with a site I trigger to assess for the presence of a supraorbital notch or foramen that must be decompressed during the primary surgery, as these structures are associated with worse migraine headache symptoms.[54]

After assessment, a surgical plan is developed that may often involve deactivation of more than one trigger site. Primary surgical evaluation and deactivation of the trigger sites as described in previous studies ensues.[13–15,18,33,53,55] Fat injection may be used during primary surgery in place of or in addition to fat pads placed in site I (frontal) and site IV (greater occipital) to restore lost volume from myectomies and to insulate the nerves to further alleviate migraine headache triggering and reduce the potential for development of a neuroma. Fat injection in site III (nasal) is not practical and the nerve is allowed to retract into the muscle in site II (zygomaticotemporal), thereby protecting the nerve and making fat injection unnecessary at this stage. An additional adjunct at this stage is corticosteroid injection. The senior author routinely injects Kenalog 40 mg/ml (Bristol-Myers Squibb, Princeton, N.J.), using a total of 0.1 to 0.3 cc through a

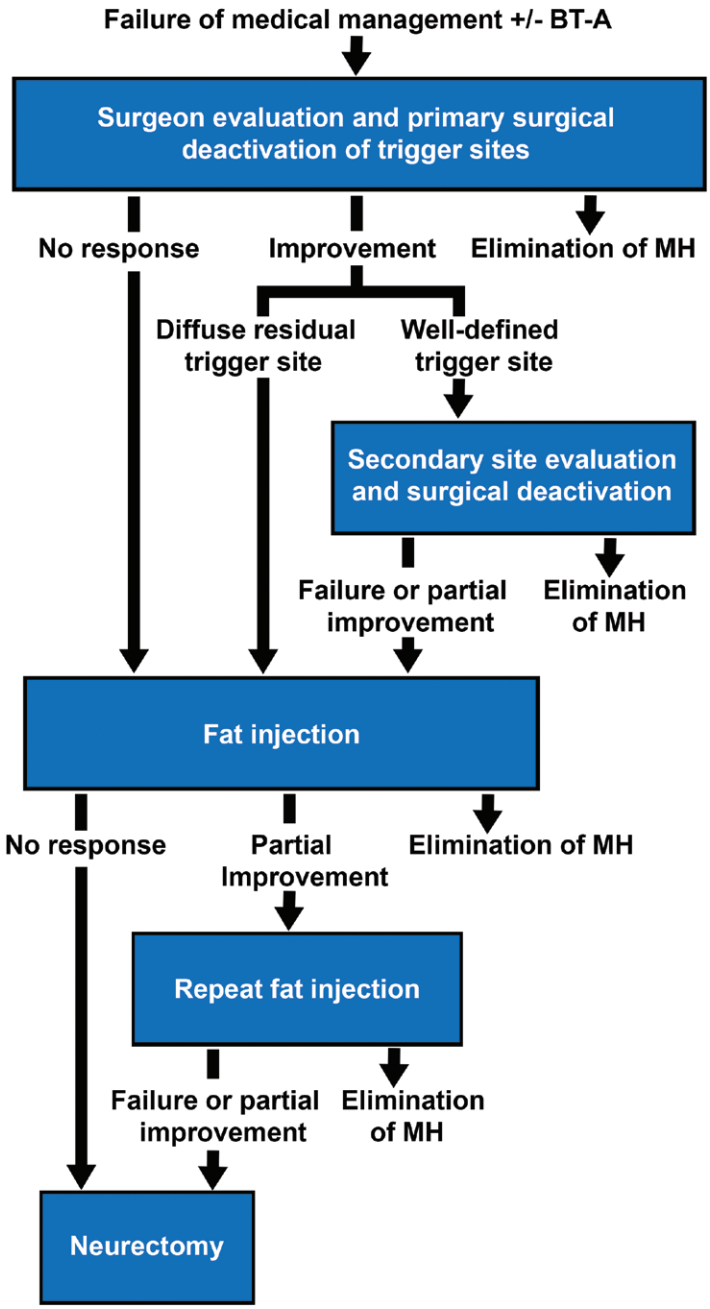

Fig. 2. Migraine headache surgical treatment algorithm. Various surgical treatments for migraine headaches are performed in the following order after the failure of medical management and botulinum toxin type A (*BT-A*) until the complete elimination of migraine headaches (*MH*) is achieved or neurectomy is performed.

30-gauge needle and a tuberculin syringe around the nerve at the end of surgical decompression for site IV (greater occipital) and site VI (lesser occipital).[25] Corticosteroids are not injected diagnostically or postoperatively. It is not uncommon that primary surgical deactivation (i.e., at frontal and occipital sites) may unmask another trigger site (i.e., auriculotemporal) that will need to undergo another round of primary surgical decompression before progressing through the algorithm.[52]

There was a wide range of timing exhibited between primary decompression and fat injection, with a minimum of 3 months between treatments in this study. It is unclear why some patients are more likely to seek a secondary procedure

sooner rather than later, and factors contributing to this decision warrant further study. Regardless, patients with no response to primary surgical deactivation are offered fat injection no sooner than 3 months after surgery to allow for postoperative inflammation to subside and for the patient's symptoms to stabilize based on our experience with migraine surgery patients over the past 18 years. Patients with improvement after primary surgery and residual pain within the same region of a trigger site that has been previously decompressed can undergo secondary-site surgical deactivation if their area of residual pain is discrete enough that the patient can point to it with one fingertip. A detectable ultrasound Doppler signal within that discrete area invariably leads to an artery that must be ligated or cauterized during secondary-site deactivation.[52,53] If the area of residual pain after primary surgery is diffuse, or if the patient does not have complete elimination of migraine headaches after secondary surgery, fat injection is indicated. Fat injection may be repeated if the patient experiences partial improvement after one round of fat injection. If the patient's migraine headaches are not completely eliminated after two rounds of fat injection or if the patient has no response to the first round of fat injection, neurectomy is indicated. Typically, neurectomy of small end branches of sensory nerves in the head and neck will result in only temporary anesthesia. Neurectomy of large, main branches is performed as a last resort, as they are more certain to cause a permanent area of numbness.[15,50] Patients should be clearly informed that a temporary or permanent area of numbness may be present after any neurectomy.

Traditionally, 73 percent of patients with migraine headaches treated with surgical decompression need multiple trigger sites (average, 2.6 sites) decompressed at the time of surgery.[56] With fat injection, most patients (76 percent) in this study needed only one site to be injected (mean, 1.28 sites injected per patient). For those without complete relief of migraine headache symptoms, we are currently studying the role and benefits of repeated fat injection. In this series of patients, fat injection was shown to be safe, with no complications (including fat embolism, hematoma, seroma, infection, or neuroma); however, patients should be counseled on the possibility of their symptoms worsening after fat injection. Intraneural injection of fat is unlikely, given the small caliber of the nerves and constant motion of the cannula during injection, thereby making this an unlikely explanation for worsened symptoms after fat injection, and no postinjection neuroma was detected on examination or found at the time of subsequent neurectomy in the patients who worsened. Most patients who experience a worsening of migraine headache symptoms following surgical decompression have been found to have a narcotic dependence.[22] Narcotic use was not investigated in this sample of fat injection patients. It is also possible that worsened symptoms continuing beyond the acute postoperative period can be attributed to progression of migraine headache abnormality or scarring after the procedure. Further study is warranted to determine the exact cause of worsened symptoms in migraine patients. Patients with a worsening of symptoms are followed monthly and evaluated clinically for neuralgia. Injection of local anesthetic can be performed to help localize a contributing nerve branch at a focal trigger site after fat injection, and neurectomy can be offered to these patients.

Two limitations of this study were the small patient sample, which may increase type II error, and lack of a randomized controlled design. Despite these shortcomings, there was a statistically significant improvement in all migraine characteristics reported by this patient sample. To assess the extent of a placebo effect, a sham surgery comparison would need to be performed. Nevertheless, it is unlikely that a placebo effect can completely account for the significant results after fat injection, considering that for their prior migraine procedure, all of these patients reported a failure of surgical treatment (i.e., recalcitrant). An additional limitation was the subjectivity of responses to the migraine questionnaire, which allowed one patient to report having one headache lasting all month, as opposed to reporting daily headaches lasting 24 hours each. Differences in reporting frequency and duration may have increased variance in the results. To account for variability in reporting frequency and duration, the migraine headache index was also analyzed. Regardless of this limitation, statistical significance was achieved for all subjective response categories and the migraine headache index in this patient sample. Subset analysis to evaluate the outcomes for each site separately was not performed because of the relatively small number of patients in each group. The three most commonly injected sites—frontal, greater occipital, and auriculotemporal—were reviewed as one group. This was a large enough powered sample, and the changes in intensity, frequency, and migraine headache index remained statistically significant ($p < 0.05$).

CONCLUSIONS

Fat injection is a relatively safe and effective adjunctive therapy for the treatment of migraine headaches in patients who are refractory to medical therapy and surgical decompression. Statistically significant reductions in intensity and frequency were achieved, with treatment success in the majority of patients.

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