Long-Term Pain Reduction Does Not Imply Improved Functional Outcome in Patients Treated With Combined Supraorbital and Occipital Nerve Stimulation for Chronic Migraine

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Background: Dual supraorbital and occipital nerve stimulation (SONS and ONS) have shown promising efficacy in treating primary headaches. However, its functional outcome is not well studied.

Objective: To present functional outcome studies of combined SONS and ONS for chronic migraine using verified metrics.

Method: Consecutive patients with both SONS and ONS assessed with Migraine Disability Assessment (MIDAS) and Beck Depression Index (BDI) both preoperatively and postoperatively were studied. Selected predictor variables included patients with ≥50% improvement of pain, disability status, number of years from diagnosis to implantation, and narcotic use. Functional outcome variables included net improvement of ranked MIDAS and BDI scores. Multivariate analysis of variance was performed to assess the correlation between the outcome and predictor variables.

Results: Sixteen patients (12 female; average age 52 years old) were studied. Follow-up ranged from 5 to 80 months (average 44.5; $\sigma = 21.4$ months). At most recent follow-up, eight patients had a positive response (≥50% improvement in headache), which was the only predictor of functional outcome (total MIDAS, MIDAS-B, and BDI) ($p = 0.021$). Of note, improvement in functional outcome was only significant during the perioperative 3–6 months period and not throughout long-term follow-up. Among the predictor variables, a strong inverse correlation was found between disability status and positive response to stimulation ($r = -0.582$).

Conclusion: There is a paucity of studies in quality of life, productivity, and psychosocial aspects with peripheral nerve stimulation therapy for headache. Patients with a positive response to SONS and ONS also reported overall improvement in their functional status as reflected by MIDAS and BDI in the perioperative period. Unfortunately, this effect waned over the long-term follow-up.

Keywords: Combined stimulation, functional outcome, migraine, neuromodulation, occipital nerve stimulation, supraorbital nerve stimulation

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INTRODUCTION

Chronic migraine (CM) is a prevalent and debilitating primary headache disorder with an annual incidence rate of 3% (1,2). Compared with the episodic form of migraine, individuals with CM suffer greater disability, more economic burden, and worse health-related quality of life (3). Furthermore, CM is associated with higher rates of major depression and suicide attempts than those found in the general population (4). Occipital nerve stimulation (ONS) was introduced in 1999 and has been shown in case series to be efficacious for migraineurs unresponsive to medical therapy (5). Numerous case series have reported promising results of ONS in treating migraine with overall efficacy of approximately 60%, (6–12) while three randomized controlled trials carried out have not shown a statistically significant difference between sham and treatment groups (2,9,13). One theory for ONS yielding variable response rates in migraine is that it may not cover the holohemispheric distribution of headache in migraine (14). Therefore, implanting both a supraorbital nerve stimulator (SONS) and an ONS for migraine and atypical facial pain has been gaining popularity (14–16).

Combined supraorbital and occipital nerve stimulation has shown promising efficacy in primary headaches, with ≥50% reduction in pain in more than 70% of patients (14,15). The benefit of a combined stimulation over single mode of stimulation (i.e. ONS alone therapy) may be explained by convergence theory of greater occipital nerve and trigeminal nerve afferents at the trigeminocervical complex (TCC). The first division of the trigeminal nerve innervates the frontal regions of the head, (17) while the greater occipital nerve provides the primary innervation for the occiput and upper posterior cervical region (18). The nexus of these two systems occurs at the TCC, which is formed by the caudal trigeminal nucleus and portions of the upper three cervical dorsal horns (19–21). The pivotal interface here is where nociceptive afferents from both the trigeminal nerve and the greater occipital nerve converge on the same second-order neurons in the TCC and thus to a final common pathway to higher centers for cephalic nociception and modulation. In 2003, Popeney and Alo suggested that this convergence at the TCC may help explain how ONS could cure pain over the distant fronto-temporal regions in migraine headaches (22). In patients with significant overlaps between the regions in TCC, stimulation at either site may produce holohemispheric pain reduction; but in individuals with poor overlaps, stimulation at one location results in partial relief. Therefore implanting stimulators at over both supraorbital and occipital nerve has a greater chance of covering migraine headaches. Among the patients who had initial implantation of ONS alone for migraine headache in our institution, significant proportions later returned opting for implantation of SONS citing that they had developed worsening headache in the frontal region over time, despite initial satisfaction with ONS.

While several institutions have published their long-term follow-up results of ONS for CM and have shown sustained efficacy over time, these reports have primarily used endpoints of decreasing headache intensity (typically ≥50% reduction in pain severity) or reduction in number of headache days (23–25). There remains a paucity of studies in quality of life, productivity, and psychosocial aspects with peripheral nerve stimulation therapy for headache. We, therefore, present long term follow-up results of functional outcomes of combined stimulation for medically refractory headaches using verified metrics.

PATIENTS AND METHODS

## Patient Selection and Data Collection

IRB permission and patient consent to perform this study was obtained IRB Control #: 10D.439. A retrospective chart review was carried out on 21 consecutive patients referred from the Jefferson Neurology Headache Clinic who had both SONS and ONS implantation at our institution between 2008 and 2014. All patients had diagnosis of CM refractory to medical managements. They were notified and consented prior to surgery that peripheral nerve stimulators are not FDA approved for treatment of migraine headaches and that there is no high level of evidence that the surgery would relieve their headaches. Only 16 who underwent preoperative and postoperative Migraine Disability Assessment (MIDAS) and Beck Depression Index (BDI) were included in this study. Six patients had unilateral implantation and ten patients had bilateral implantations. Patients did not receive psychological testing prior to the implantation. None had preoperative narcotic medication use. The MIDAS and BDI scores were collected by neurology headache clinic before and after the implantation, typically in three month intervals.

The MIDAS score consists of three scores: total MIDAS, MIDAS-A, and MIDAS-B. Total MIDAS is the sum of five questions asking for functional capacity/productivity of a patient at work and home in the past three months; MIDAS-A is the number of headache days in the past 90 days; and MIDAS-B is the pain scale of 0–10 describing the average severity of headache in the past 90 days. Meanwhile, BDI is a self-assessment of depression consists of 21 multiple choices with scores ranging from 0 to 63 with higher numbers indicate severer depression. Both MIDAS and BDI have been used as valid self-assessment questionnaires for migraine patients (26,27).

Surgical Implantation

Under general anesthesia, the patient was positioned in a lateral position with their head in a horseshoe-shaped head holder. After prepping and draping the ipsilateral forehead, neck, and chest, the incision site, and needle insertion site were marked. For SONS, one incision was made behind the hairline approximately 1.5 cm superolateral to the lateral aspect of the eyebrow for introduction of a Tuohy guide needle or a percutaneous peel-away introducer sheath. Another incision was made in the posteriorly in the temporal region, to which the distal SONS wire was tunneled. The Tuohy needle was prebent to the curvature of the forehead and inserted such that the electrode contacts were positioned perpendicular to the course of the supraorbital nerves. A standard electrode (typically eight contact electrodes were used) was passed into the epifascial plane, and the tip of the electrode was buried subperiosteally to hold the tip down. After removing the guide needle, the electrode was tunneled back to the incision in the temporal region, a strain-relief loop was created and a titanium dogbone-shaped mini-plate was used to anchor the electrode to the cranium. Subsequently, the distal wire was tunneled down to the neck behind the ear.

For ONS implants, the path of the occipital artery was marked with the assistance of Doppler ultrasound. A separate incision was placed behind the mastoid process and the electrode was tunneled to the midline, across the path of the occipital nerve, using the appropriately bent Tuohy needle while aiming along the level of the C-1 arch. After the electrode was placed, a strain relief loop was created, tucked into the subcutaneous fascia and anchored. Last, an implantable pulse generator (IPG) pocket was made in the buttocks, subclavicular region, or abdomen (ipsilaterally), based on the patient's preference. In our experience, IPG sites closer to the lead (i.e., infraclavicular region) are associated with lower adverse event
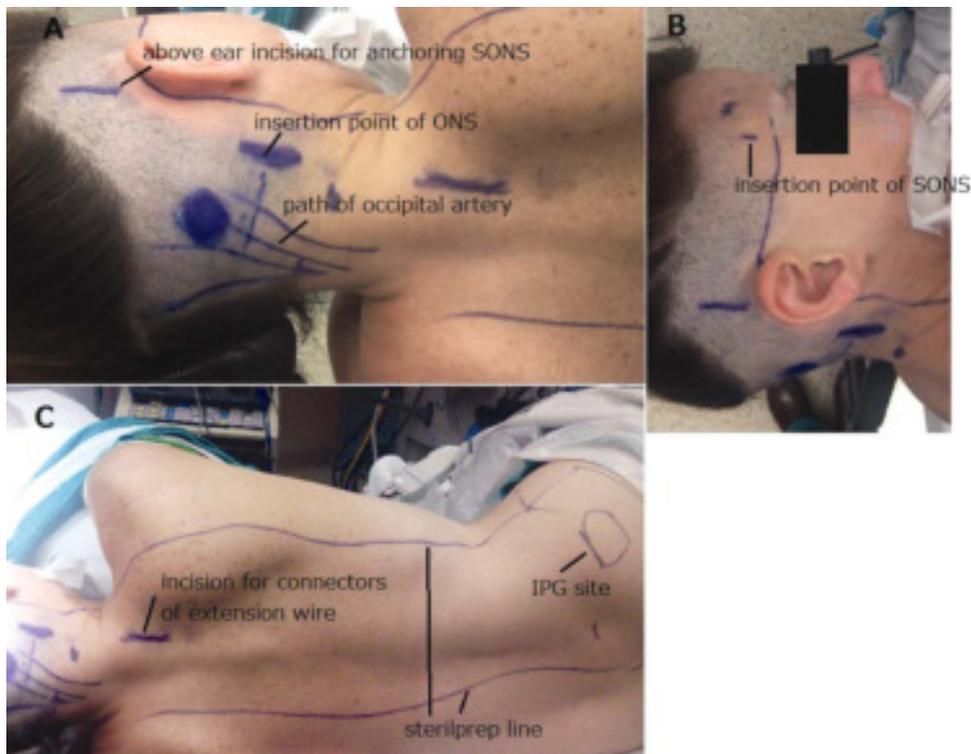
Figure 1. Locations of incisions for ONS electrode (A), SONS electrode (B), battery, and connecting extension wires (C) when performing right-sided SONS and ONS implantation. A patient may be brought back for opposite side of electrodes and battery placement at a later date.

incident rates such as lead migration and discomfort requiring reoperation (28). In general, we used rechargeable batteries. Both leads from SONS and ONS were tunneled down to the pocket, and the battery was inserted (Fig. 1). Postoperative x-rays were obtained to confirm the locations of the leads (Fig. 2).

Data Collection and Analysis

Pain severity was recorded from two-week and two-month follow-up visits as visual analogue scale (VAS). These results were compared to the preoperative VAS to obtain short-term efficacy in pain reduction. Long-term follow-up of headache severity in VAS was obtained along with MIDAS and BDI scores at approximately three months interval follow-ups. Selected predictor variables included patients with $\geq$50% improvement of VAS, disability status, number of years from diagnosis to implantation, and narcotic use. Functional outcome variables included net improvement of ranked total MIDAS, MIDAS-A, MIDAS-B, and BDI.

Statistical analysis was performed with IBM SPSS Statistics 22. A general linear model multivariate analysis of variance (MANOVA) was performed to account for the correlation between the

Figure 2. Postoperative skull radiograph (left, AP view; right, lateral view) showing right sided occipital and supraorbital leads anchored with a dog bone–shaped plate.

Table 1. Break Down of Efficacy Based on Short-Term and Long-Term Follow-Up.

Efficacy	Short-term*	Long-term**	Device removed to date
Positive	12	8	0
Negative	4	8	5
% efficacy	75%	50%	31.2%

Efficacy rate dropped from 75% to 50% overtime. All four patients converted to negative responders happened during the first year of implantation. Five of the negative responders had the device removal secondary to malfunction and discomfort.
*Collected two months postoperatively.
**Collected from most recent follow-up.

outcome variables. Analysis of MIDAS and BDI was performed with preoperative VAS, postoperative VAS within two months, and long-term postoperative VAS to evaluate both short- and long-term impact.

RESULTS

Analysis of Short-Term and Long-Term Efficacy

Sixteen out of the 21 patients identified had complete preoperative and postoperative MIDAS and BDI scores. Twelve of them were females and four were males. Short-term follow-up of approximately two months demonstrated a response rate of 75%, with 12 out of 16 patients having positive response. Long-term follow-up ranged from five to 80 months with an average follow up of 44.5 months ($\sigma = 21.4$ months). At most recent follow-up, eight had a positive response—defined by $\geq$50% improvement in headache severity; while the other eight had <50% reduction and were considered poor responders. Table 1 summarizes the change in efficacy between the short- and

long-term follow-ups. All four subjects that transitioned from a positive responder to a poor responder perceived their change in response within the first year after implantation—during months 4, 7, 8, and 12, respectively. Table 2 is the comprehensive summary of each patients' baseline data, long-term efficacy response, and functional outcome data at immediate postop as well as most recent follow-up. Of the eight poor responders, five had stimulators removed to date while the remaining three continue to use stimulation. Patients remained on same regiment of migraine medications prior to and after implantations. No narcotics were used by any patients during the follow-up period. The main adverse events included lead migration (42.8%), supraorbital lead allodynia (21.4%), and infection (14.2%) with a resulting high reoperation rate (35.7%). Reoperations were more frequent among negative responders than positive responders (67% vs. 33%).

Analysis of Functional Metrics

When analyzing the correlation of positive response to each outcome variable separately, there were suggestive trends between positive response and improved functional outcome; however, none were statistically significant ($p = 0.137$ for total MIDAS, $p = 0.072$ for MIDAS B, and $p = 0.064$ for BDI) (Fig. 3). MIDAS-A was not a distinguishing variable in the statistical analysis. The reason for univariate analysis above showing no statistical significance is due to low power of the study secondary to small sample size (only 16 patients). Therefore, to increase the power of the statistical analysis, we increased the variance of the study by conducting multivariate analysis next. This is to evaluate whether combined outcomes of improvement in MIDAS and BDI had causal relationships with the positive pain efficacy. Multivariate analysis of the perioperative functional metrics (MIDAS and BDI) typically assessed within three to six months before and after surgery, demonstrated that a positive response ($\geq$50% improvement in pain) was significantly correlated with the reverse rank of net improvements in total MIDAS, MIDAS-B, and BDI scores combined ($p = 0.021$) (Fig. 4). A positive response was

Table 2. Summary of Patient's Baseline Data and Follow-Up Points for Efficacy and Functional Outcome Scores.

Patient age/sex	Diagnosis	Years of diagnosis before implantation	Narcotic use prior to surgery	Disability status	Length of follow-up (month)	Positive efficacy at the most recent follow-up?	Changes in tMIDAS (preop / postop / most recent f/u)	Changes in BDI (preop / postop / most recent f/u)
27/F	CM	7	None	No	38	Yes	83 /19 / 79	21 / 11 / 18
33/M	CM	10	None	No	39	Yes	85 / 23 / 67	19 /18 / 24
54/F	CM	20	None	Yes	29	Yes	157 / 27 / 140	19 / 7 / 32
34/M	CM	8	None	No	51	Yes	21 / 4 / 36	6 / 1 / 6
50/F	CM	14	None	No	27	Yes	100 /110/ 90	11 / 4 / 8
28/F	CM	6	None	No	5	Yes	360 /14 / 220	11 / 1 /3
49/F	CM	15	None	No	33	Yes	24 / 25 / 28	13 / 8 / 15
38/F	CM	3	None	No	30	Yes	91 / 23 / 85	21 / 4 / 24
44/F	CM	4	None	Yes	56	No	143 /120 / 150	10 / 11 / 13
39/F	CM	9	None	Yes	65	No	120 / 145 /150	14 / 19 / 20
42/M	CM	16	None	No	58	No	95 /145 / 130	8 / 7 / 25
48/F	CM	15	None	No	80	No	200 /130 /200	26 / 30 /34
56/M	CM	13	None	Yes	47	No	107 /135 / 150	5 / 19 / 24
60 /F	CM	17	None	Yes	60	No	115 / 110 / 150	34 /18 / 36
54/F	CM	22	None	Yes	48	No	32 /110 /90	4 / 6 / 2
52/F	CM	16	None	Yes	38	No	120 / 180 / 190	15 / 17 / 22

Positive efficacy: 50% benefit per patient or verbiage in the medical record suggesting significant improvement.
F, female; M, male; CM, chronic migraine; tMIDAS, total MIDAS score.

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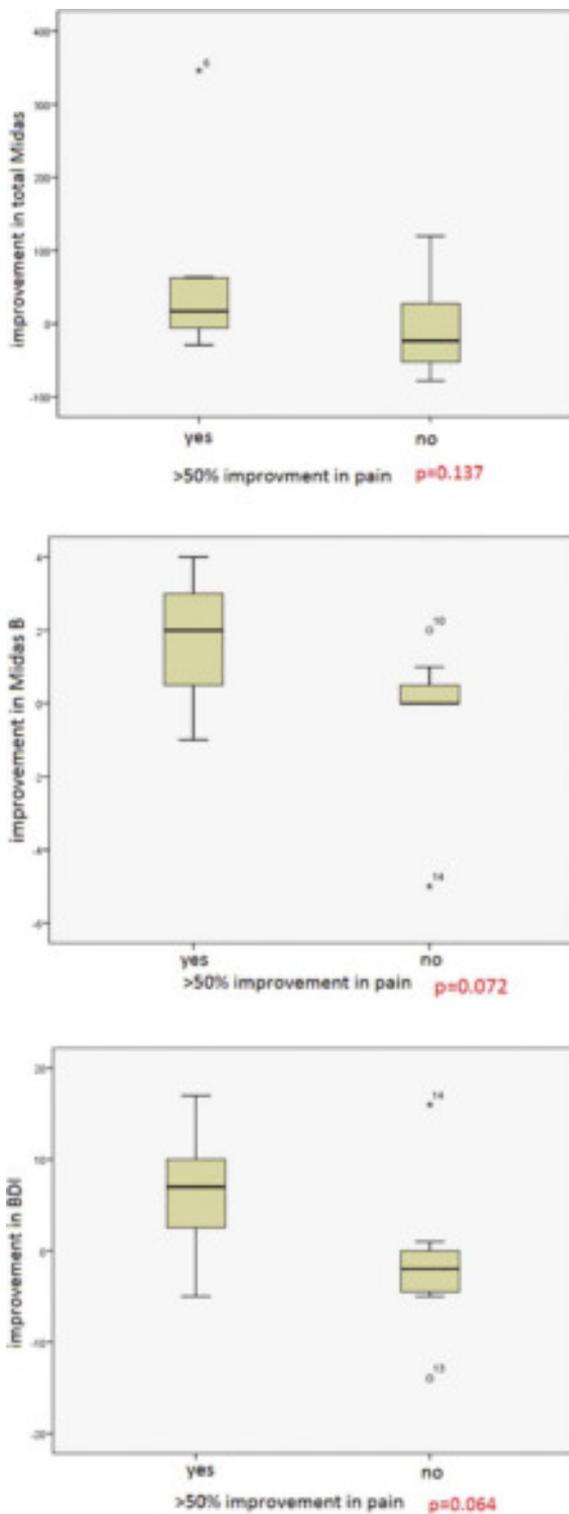
Figure 3. Each box plot shows ≥50% improvement of pain as a potential predictive factor of outcome variables: total Midas, Midas B, and BDI, respectively, from top to bottom. There were strong trend in correlation but none reached statistical significance as shown on each *p*-value. This is likely due to small sample size induced low power of the study as well as increased variance of the data when analyzing single outcome variables as opposed to multivariate analysis.

found to be the only positive predictor of functional outcome, but only in the immediate perioperative period and not for long-term postoperative scores. Subgroup analysis of the posi-

tive responder cohort demonstrated that the loss of functional improvement was not associated with a loss of pain control. While, positive responders continued to report ≥50% improvement in pain, their long-term functional scores reported varied independently of these pain scores (Fig. 5).

Analysis of Predictor Variables

Analysis between predictor variables demonstrated a strong inverse correlation between disability status and positive pain relief (≥50% pain reduction) ($r = -0.582$). No other predictor variables—namely age, sex, age of onset to implantation, number of years from diagnosis to implantation, and narcotic use—had strong correlation with each other.

DISCUSSION

Two key findings are presented in this study: 1) Combined ONS and SONS improves overall quality of life and depression outcomes in those with positive response to pain reduction; and 2) This improvement in our cohort is only significant during the perioperative period and the effect waned over time due to loss of association between the pain scores and functional scores reported by the patients during long-term follow-up.

Due to the small sample size induced low study power, we were not able to establish direct correlation between pain efficacy and MIDAS scores or BDI scores individually. However, we did find suggestive trend in positive pain efficacy and improvement in MIDAS B and BDI ($p = 0.072$ and $p = 0.064$, respectively). To increase the power of the study, we carried out multivariate analysis and found that for those who had overall improvement in all of total MIDAS, MIDAS B, and BDI immediate after postoperatively to have causal relationship with positive pain efficacies.

In addition, when all postoperative combined MIDAS and BDI scores were compared with preoperative scores, these improvements were not observed. Differences in functional metrics were greatest at the time closest to surgery—with patients typically
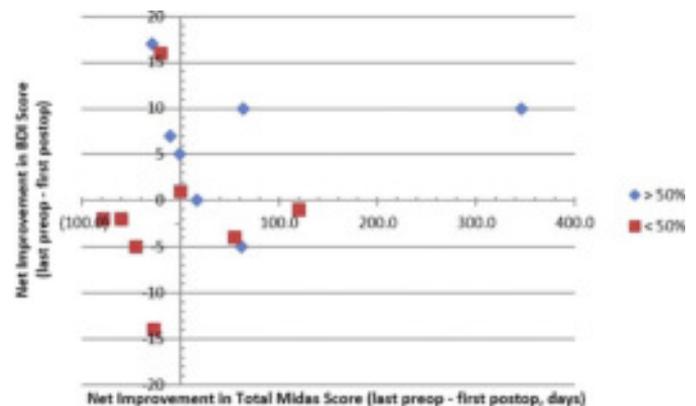
Figure 4. Graphical representation of multivariate analysis showing positive/negative pain efficacy vs. combined MIDAS and BDI outcomes. Blue diamond shows eight patients with good stimulation results having both improved BDI score on the *y*-axis and improved total MIDAS score on the *x*-axis in this descriptive statistics during the perioperative period. On the other hand, red squares show eight patients with poor stimulation results having corresponding worsening of total Midas on *x*-axis and negative improvement on BDI in *y*-axis. This linear regression of ≥50% improvement in headache pain with the combined scores in BDI, total MIDAS, and MIDAS-B (not graphed) was statistically significant ($p = 0.021$).

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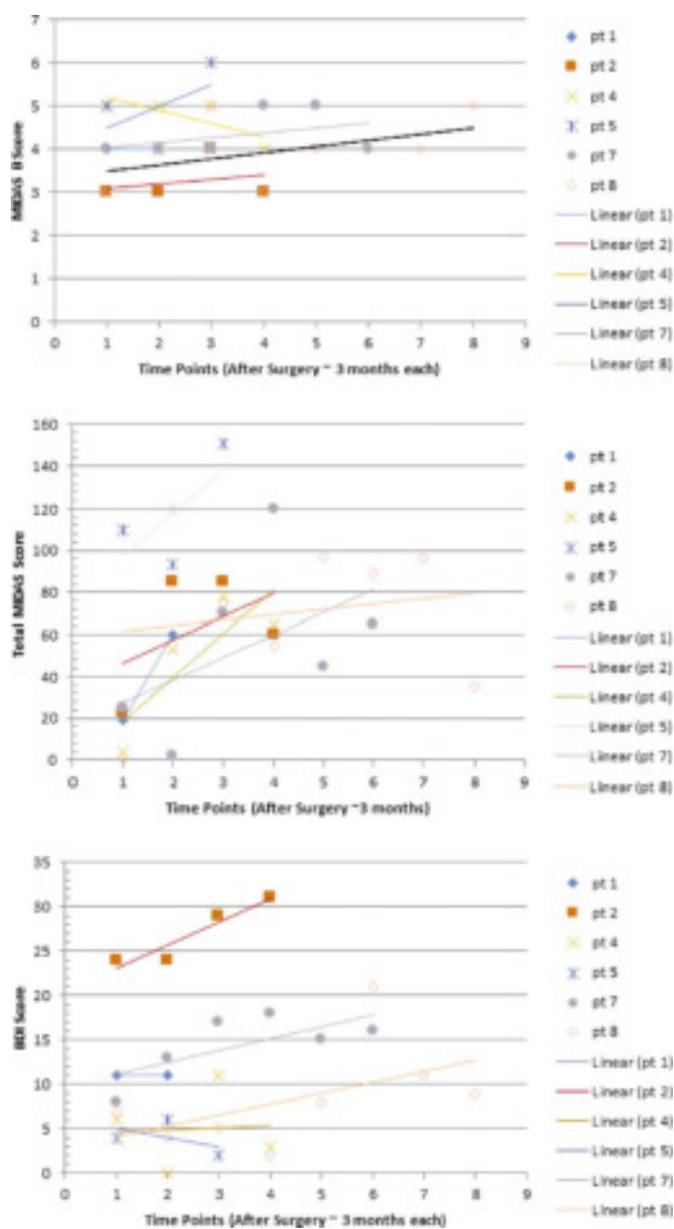
Figure 5. Subgroup analysis of relationship between pain severity (MIDAS-B) vs. functional and depression outcomes (total MIDAS and BDI) in positive responders. Follow-ups among these patients ranged from two to eight questionnaires with three-month intervals. Top graph shows that MIDAS-B (equivalent to VAS) showed minimal change over the follow-ups while middle (total MIDAS) and bottom (BDI) reported varied significantly over the follow-ups independently of reported pain scores.

reporting the worst pain and depression before surgery and perceiving the maximal benefit right after surgery with this effect generally dissipating over time.

Functional and Psychological Outcome Studies of PNS for Migraine

Given the disabling nature of CM and the ensuing economic burden for both the patient and society, we focused on MIDAS and BDI to measure impact on quality of life following implantation. Existing research on the functional outcome of ONS is limited in both sample size and follow-up duration. This is the first report of quality of life assessment for combined stimulation for migraine.

There are four long-term follow-up studies of ONS efficacy with some functional outcome data published to date (Table 3). Among these four studies, the efficacy of pain control ranged from 42 to 67%, which is comparable to our efficacy rate. The follow-up ranged from 13 to 36 months, which was shorter than our average follow-up of 44 months. The only study with statistically significantly improved functional outcome was by Schwedt et al. (7) in which the average MIDAS, BDI, and HIT-6 of patients preoperatively and post-operatively had statistically significant improvement. All four studies focused on long-term efficacy rather than functional outcome with only one set of preoperative and postoperative functional assessments thereby limiting their ability to comment on long-term functional outcomes. In our patient group, positive responders to combined stimulation had significant functional improvement in daily activity and depression. Unfortunately, this effect was not long lasting secondary to variability in patient reporting of functional scores despite stable pain scores. No other data has been published to echo this finding so far.

In this study, we analyzed whether any predictor variables had significant correlation with improvement in MIDAS and BDI and found that only ≥50% improvement in pain severity was a predictive factor for the improved perioperative functional outcomes. This correlation was only found when MANOVA was carried out with combined total MIDAS, MIDAS-B, and BDI in the immediate perioperative period. When we looked at each of the metrics separately, there was a suggestive trend ($p = 0.137$, $p = 0.072$, and $p = 0.064$) with the positive response in reduction of pain, but they were not statistically significant. This finding is likely due to increased statistical power provided by the MANOVA analysis, accentuating the effect size.

More importantly, the reduction in functional outcomes was only significant in the immediate perioperative period and was lost with long-term follow-up. The gradual decline in desirable response to peripheral nerve stimulation (PNS) overtime has been attributed to loss of the "honeymoon effect," (29) the natural history of CM, (30–33) and poor understanding of optimal stimulation parameters for migraine. These explanations, however, do not entirely explain the dissociation between reported pain scores and functional outcomes we observed in this cohort. The reason for variable and worsening trends in total MIDAS and BDI reported over the long-term follow-ups despite stable VAS is unclear—but suggests that there are complex factors affecting migraineurs' functional status aside from the pain they perceive.

Limitations of the Study

The retrospective data collection and small number of patients having functional outcome data largely limit the result of this study. Although we selected MIDAS and BDI, there is no consensus as to what are the ideal functional metrics assessing patients who are treated with PNS. A prospective registry to collect consistent data from a larger patient population can possibly mitigate these limitations. Until further efforts in collecting clean data within a larger cohort of patients can be conducted, the functional benefit from the stimulation of migraine will remain difficult to assess. Further research in identifying appropriate functional metrics for stimulation therapy as well as optimum stimulation parameters that benefit patients over long-term are also necessary to help advance this field.

Table 3. Literature Review of Long-Term Follow-Up of ONS for Migraine With Functional Data Published to Date.

Authors	Pub year	Study type	No. of pt	Length of follow-up	Pain efficacy	Functional outcome measure and results
Verrills P	2014	Retrospective review	60	Avg. 12.9 ± 9.4 mo.	67.2% positive	Neck disability index and Zung depression index showed trend in improvement postoperatively but only one set was collected postoperatively without mention of at which point of follow-up these were obtained.
Palmisani S	2013	Retrospective review	25	Avg. 36 ± 23 mo.	53% positive	Only seven patients (28%) had functional outcome follow-up and their BDI and TSK improved independent of pain efficacy.
Brewer AC	2013	Retrospective review	14	Range 1–70 mo.	42% positive	MIDAS score decreased by 49.9% in positive responders.
Schwedt TJ	2007	Retrospective review	15	Avg. 19mo. (5–42mo.)	60% positive	Statistically significant improvement in MIDAS, BDI, and HIT-6 between baseline mean and follow-up mean ($p < 0.03$).

Pub year, publication year; pt, patients, avg., average; mo., months.

CONCLUSION

In this long-term follow-up of retrospective functional outcome analysis of the CM patients treated with combined SONS and ONS, patients with ≥50% improvement in pain demonstrated a statistically significant correlation with overall improved functional outcomes of MIDAS and BDI scores, suggesting that patients who respond to PNS for headache also have a subjective improvement in quality of life. Unfortunately, this improvement was only significant during the short-term follow-up and the effect waned over time. Functional status of migraineurs are likely affected by complex factors in addition to their perceived pain severity. Thus, creating appropriate metrics of quality of life for stimulator populations is one of the challenges that lie ahead.

Authorship Statements

Dr. Clark designed and conducted the study, data collection, and drafting the manuscript. Drs. Chalouhi and Zanaty helped with data collection and reviewed the manuscript. Dr. Wu was the primary editor of the manuscript draft. Mr. Boorman was the statistician who conducted the data analysis. Dr. Sharan supervised and approved the final, edited manuscript. All authors approved the final manuscript. No funding was provided for the study.

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