

# Peripheral Nerve Field Stimulation for Chronic Headache: 60 Cases and Long-Term Follow-Up

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**Objective:** The objective of this study is to evaluate the efficacy of peripheral nerve field stimulation (PNFS) for the treatment of chronic headache conditions.

**Materials and Methods:** For more than a four-year period, 83 patients underwent a trial of a PNFS system targeting the nerve regions including occipital and supraorbital and infraorbital nerves, which best corresponded with their area of head pain. Sixty patients reported a successful trial and underwent a subsequent implant of the PNFS system. Questionnaires, along with patients' charts, were used to assess outcomes as follows: pain (11-point numerical pain rating scale), analgesic use, depression (Zung Depression Scale), disability (Neck Disability Index), patient satisfaction, and surgical complications. Patients were followed up for an average of  $12.9 \pm 9.4$  months (range 3–42 months).

**Results:** An average pain reduction of  $4.8 \pm 2.3$  pain scale points was observed (preimplant  $7.4 \pm 1.6$ ; follow-up  $2.6 \pm 2.1$  [ $p \leq 0.001$ ]). Of the 60 patients implanted, 41 reported >50% pain relief. Medication use was reduced in 83% of patients who were previously taking analgesics or prophylactic medications. Similarly, reductions in degree of disability and depression also were observed. Of the 60 cases, ten surgical revisions were required; however, no long-term complications were reported.

**Conclusions:** PNFS for chronic headache is an evolving therapy. This study demonstrates that this reversible and effective treatment can be a promising pain relief strategy for this often intractable condition.

**Keywords:** chronic pain, headache, migraine, neuromodulation, occipital nerve stimulation, outcome measure, peripheral nerve field stimulation

**Conflict of Interest:** Paul Verrills is an *ad hoc* peer–peer consultant and lecturer for St. Jude Medical Pty Ltd, Spinal Modulation Corp., Nevro Corporation, and Medtronic Inc., and is a member of the Boston Scientific Pty Ltd. Medical Advisory Board. Bruce Mitchell is an *ad hoc* peer–peer consultant and lecturer for St. Jude Medical Pty Ltd, Nevro Corporation, Medtronic Inc., and Boston Scientific Pty Ltd. Paul Verrills, David Vivian, Bruce Mitchell, and Adele Barnard are shareholders of Clinical Intelligence Pty Ltd.

## INTRODUCTION

Headache is caused by activation of cranial nociceptors and can largely be classified as either primary (where there is an inherited tendency) or secondary (where outside factors such as trauma and infection are thought to contribute). Of the primary headache disorders, migraine is the most common. Despite the plethora of interventions available ranging from serotonin and 5-hydroxytryptamine receptor agonists to beta and calcium channel blockers, coupled with therapies such as trigger avoidance, headache disorders often remain refractory to medical treatment (1).

Given this, recent interest has focused on the minimally invasive and reversible procedure of subcutaneous peripheral nerve field stimulation (PNFS) for the treatment of chronic craniofacial pain. Initially, PNFS was applied to the occipital and high cervical spine regions (2–7). Increasingly, the frontal and supraorbital regions are targeted for cluster headaches and migraines and headaches associated with fibromyalgia (8–16), often combined with leads stimulating the occipital nerve region (9,17). The use of PNFS to stimulate branches of C2–C3 in the occipital region was documented as early as 1977 in a series of six patients (18), but it only gained momentum in 1999 when reported by Weiner and Reed. In this study, it was

noted that direct nerve contact was not vital for pain relief in the region of paresthesia, as subcutaneous tissue was capable of conducting electrical impulses in a dermatomal and/or myotomal distribution (18). Other stimulation device-based therapies for headache, such as deep brain stimulation, are outside the scope of this paper and are covered thoroughly elsewhere (19–21).

The mechanism by which PNFS results in pain relief is poorly understood, and likely to be because of a number of interlinking mechanisms. Matharu and colleagues have suggested that PNFS may reduce headache severity by altering regional cerebral blood

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flow in the dorsal rostral pons, thus modifying thalamic activation (22). A more recent study, also using positron emission tomography, has suggested that occipital nerve stimulation (ONS) may restore balance to deficient antinociceptive pathways. This was demonstrated by the presence of hyperactivity in the perigenual anterior cingulate cortex of responders, a pivotal structure in the endogenous opioid system, compared with minimal activity in nonresponders (23). The exact mechanism of PNFS will become clearer as understanding of its efficacy and physiologic effects grows. Despite the theoretical vacuum, a small but growing body of circumstantial evidence supports the future clinical use of PNFS for the treatment of intractable headache.

Published cohort findings (ranging between 10 and 25 patients each) have demonstrated average improvements in pain relief of 70–95%, coupled with reductions in headache days per month and reduced prophylactic and/or analgesia medication use (5,13,24–27). Three-month data from the multisite, randomized ONSTIM study have further strengthened the evidence for ONS in headache disorders. Patients in the active adjustable stimulation group ( $N = 28$ ) reported a 27% reduction in headache days per month and an average reduction in pain intensity of 1.5 on the visual analogue scale, compared with 8.8% and 0.5, respectively, in the preset stimulation group ( $N = 16$ ) (28). Lastly, in a recent randomized, multicenter, double-blinded, controlled study, 66% of all patients at the one-year follow-up reported good to excellent pain relief, whereas a similar 68% stated an improvement in quality of life following their implant. Interestingly though, during the initial 12-week blinded phase where the sham group was yet to have their PNFS systems activated (systems were activated at the 12-week visit), no significant difference in responder rates was observed (29). Given these reports, and the general shortage of larger cohort and extended follow-up studies, we prospectively followed 60 consecutive patients, following PNFS implantation for headache disorders, as classified by the International Headache Society diagnostic criteria. The objective of this study is to assess reductions in pain, analgesic use, and disability, along with complication rates.

## METHODS

### Patient Population

Sixty consecutive ONS permanent implant patients (23 men, 37 women) with a mean age of  $52.9 \pm 13.3$  years met our eligibility criteria.

To be eligible for implantation, patients had to meet the International Headache Society diagnostic criteria with emphasis on the following criteria:

- chronic daily headache, occipital neuralgia, or chronic migraine
- failure to respond to other conservative treatments (including medications, psychological therapies, rehabilitation, interventional pain procedures, and pain management programs)
- psychological clearance (including drug addictions, major depression, and similar severe disorders that might impact on successful treatment)
- successful trial phase (>50% pain relief, improvements in daily activities)
- informed consent

### PNFS Trial Procedure

Routine sterile preparation and draping took place for each patient in the operating room. Patients were administered preop-

erative intravenous antibiotics (1 g cefazolin, ACS Dobfar SpA, Tribiano, Italy). Leads (St. Jude Medical Neuromodulation, St. Paul, MN, USA; Boston Scientific, Natick, MA, USA; or Medtronic, Minneapolis, MN, USA) were placed subcutaneously within the maximal area of pain via 14-Ga Angiocaths (Becton Dickinson, Mexico DF, Mexico). Further, it was our view that it was the area that the patient felt the pain that was most relevant and not the proposed underlying diagnosis. With this in mind, we then targeted the nerve regions including occipital and supraorbital and infraorbital nerves, which best corresponded with their area of head pain. On-table stimulation confirmed that the leads were placed in the correct anatomic area and were comfortable. The leads were stitched to the skin using 2/0 black silk suture. Dressing was then applied, and the leads were taped. Each patient was monitored for 90 min in the recovery suite following the procedure. Patients were prescribed postoperative cephalexin for ten days and remained in hospital for regular monitoring for two nights. Following programming of the stimulator, patients were permitted to adjust their stimulation voltage and switch the stimulator on and off as required throughout the trial period. The leads were then removed in the day surgery unit six to ten days later. A successful PNFS trial was defined by 1) a reduction of at least 50% of the original pain; 2) total or near total stimulation coverage of the painful region; 3) a reduction of reliance on analgesics and improvements in valued activities of daily living. Those patients reporting a successful trial phase proceeded to implantation. Equipment was sourced from either St. Jude Medical Neuromodulation, Boston Scientific, or Medtronic.

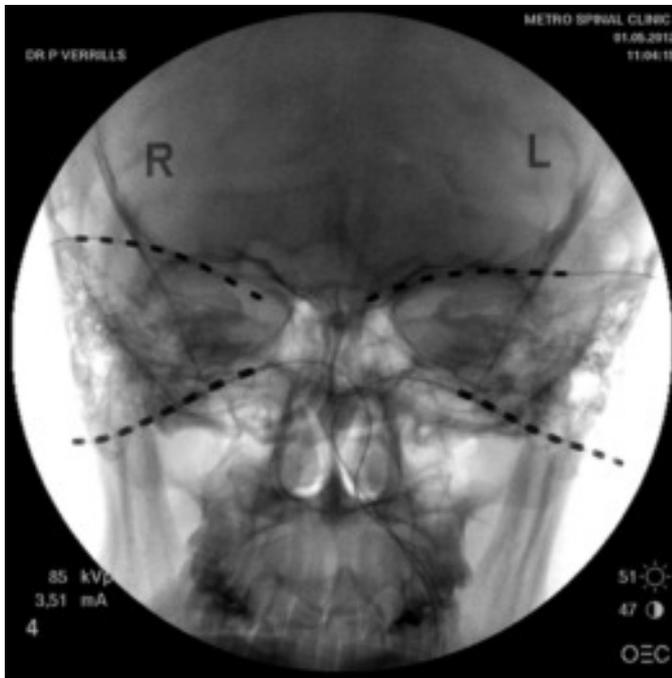
### PNFS Implantation Procedure

Routine sterile preparation and draping took place for each patient in the operating room. The patient's skin was marked under fluoroscopy, based on successful trial position. Patients were administered preoperative intravenous antibiotics (1 g cefazolin). A small incision was made, the site checked for good hemostasis, and the implantable pulse generator (IPG) pocket which was created in the appropriate area for each individual patient (e.g. upper buttock; lateral chest wall, upper chest, below the axillary region) packed with plain gauze squares. Following incisions, 14-Ga angiocaths or the introducers that were provided with the lead tool kits were used to place the leads within the specific areas identified at each individual patient's trial (Fig. 1). Live C-arm fluoroscopy screening ensured adequate positioning of the implant. The leads were anchored into position with a restraining loop using O-Silk (PERMA-HAND Silk Sutures, Ethicon Inc., Somerville, NJ, USA), and tunneling took place to the IPG pocket. Leads were attached to the IPG, screws were tightened after fluoroscopy, and impedance checks and on-table stimulation confirmed that the leads were adequately sited. Sites were checked for good homeostasis, following which the wounds were closed in layers with 2/0 VICRYL™ sutures (Ethicon Inc., Somerville, NJ, USA) and subcutaneous MONOCRYL™ (Ethicon Inc., Somerville, NJ, USA). Patients were prescribed postoperative cephalexin for ten days and remained in hospital for regular monitoring for two nights. Patients were reviewed 48 hours later in the consulting rooms.

### Outcome Measures and Statistical Analysis

Ethics approval to perform the data collection was obtained from The Avenue Human Research Ethics Committee.

A follow-up rate of 100% was obtained for pain scores measured using the 11-point numerical pain rating scale (NPRS) and complication rates. Online questionnaires using the Clinical Intelligence data collection software system, along with the patients' charts, were used to assess the following measurements:



**Figure 1.** Live C-arm fluoroscopic image of a bilateral supraorbital and occipital nerve lead placement.

- analgesic use
- depression (Zung Depression Index [ZDI])
- disability (Neck Disability Index [NDI])
- patient satisfaction

Statistical analysis was performed using the nonparametric, unpaired Mann–Whitney *U* test and paired samples *t*-test, with a *p* value of <0.05 considered statistically significant. Pearson chi-squared test was used to look at relationships between outcome variables. These tests were performed using IBM SPSS Statistics 18 (IBM, Armonk, NY, USA).

## RESULTS

Overall, 83 consecutive patients underwent a PNFS trial procedure. Sixty patients met the criteria of a positive trial phase and proceeded to implantation, resulting in a trial to implant conversion rate of 72%. The 60 patients receiving a permanently implanted system were observed for an average of  $12.9 \pm 9.4$  months (range 3–4 months). Of the 60 implants, 50 targeted the occipital nerve regions, three implants targeted the supraorbital and infraorbital nerves, whereas the remaining seven implants targeted a combination of the occipital supraorbital and infraorbital nerve regions.

### Pain Indices

A statistically significant reduction of  $4.8 \pm 2.3$  pain scale points was observed (preimplant pain score of  $7.4 \pm 1.6$  compared with a follow-up average of  $2.6 \pm 2.1$  pain scale points) ( $p \leq 0.001$ ) (Table 1). Pain relief was calculated as a proportion of the difference in pain scale points prior and following implantation. Patients receiving  $\leq 24\%$  pain relief or 25–49% pain relief were classified as attaining a poor or fair response, respectively, whereas a 50–74% result

reflected a good response, and 75–100% improvement in pain denoted an excellent response. An excellent response was reported by 23 patients, whereas 18 patients reported a good response. Overall, 41 of the 60 implanted patients (and of 83 trialed patients) experienced pain relief greater than 50%. A fair response to pain relief was observed in ten patients, and the remaining nine patients reported poor results to PNFS. Of these nine patients who reported “poor” pain relief, only one patient did not experience any pain relief; the remaining eight patients reported a minimal reduction in their pain score of  $1.3 \pm 0.7$  NPRS. These patients also responded poorly to the analgesic and satisfaction parameters described below.

### NDI and ZDI

Given the physically and psychologically disabling nature of chronic headache, patients were asked to complete the self-assessed NDI and ZDI prior to implantation and at follow-up. Patients reported an improving trend in both the disability and depression scales following implantation (Table 1).

### Medication Use

Thirty-five of the patients in our cohort of 60 reported using prophylactic medications or symptom-related analgesics prior to undergoing a PNFS implant. Patients were asked to report whether they had observed a change in their use of these medications following the PNFS implant. A Likert scale with the following options was given to the patient: not applicable, unsure, no change, increased, slight decrease, moderate decrease, or extreme decrease. An overwhelming 29/35 patients reported some degree of medication reduction, with 15 patients reporting the decrease as extreme, citing a complete stop in analgesic use. Five patients reported no change in their medication use, whereas one patient reported an increase in their medications (Fig. 2). These six patients also reported poor pain relief following PNFS. Decrease in analgesic use was correlated with increased pain relief ( $r = 0.517$ ,  $p = 0.001$ ).

### Patient Satisfaction

Patient satisfaction was determined by the following scale: completely satisfied, very satisfied, satisfied, not completely, or unsatisfied. Fourteen patients were completely satisfied with their outcome, with a combined 50 patients either satisfied, very satisfied, or completely satisfied with their outcome (Fig. 3). Of the ten patients who were either not completely satisfied or unsatisfied, poor responses to the previous outcome variables prevailed. Patient satisfaction highly correlated with pain relief ( $r = 0.783$ ,  $p \leq 0.001$ ).

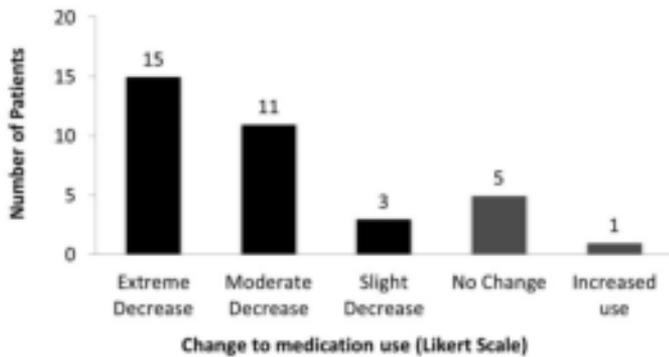
### Complications

Complications were monitored and collected for all 60 patients (Table 2), and 14 patients reported a complication. There were seven hardware (lead and/or IPG) erosions, one hardware failure, one lead migration, and one case where there was not enough redundancy in the implanted leads resulting in the leads pulling and feeling tight during hyperextension. All but one of these cases had their systems repositioned, reimplanted, or replaced with positive outcomes. Four cases of infection were noted, and one case in particular occurred one year post implant following minor trauma over the occipital lead area. Out of the 60 patients receiving a permanent implant, only four patients had their systems explanted because of a complication.

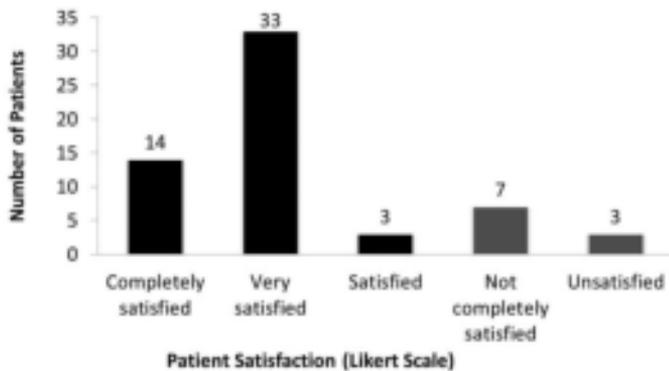
**Table 1.** Outcome Measures Following Occipital Nerve Stimulation.

Variable	Pre-PNFS Mean (SD)	Post-PNFS Mean (SD)	Difference Mean (SD)	p Value
Pain (NRS)				
<6 months follow-up (N = 9)	7.1 (1.8)	3.1 (1.8)	4.0 (2.2)	<0.001
6–11 months follow-up (N = 27)	7.6 (1.5)	2.7 (2.1)	5.0 (2.4)	<0.001
12–23 months follow-up (N = 16)	7.1 (1.7)	2.5 (2.6)	4.6 (2.6)	<0.001
24–35 months follow-up (N = 3)	6.5 (0.7)	1.3 (1.0)	5.2 (0.3)	0.024
36–42 months follow-up (N = 5)	8.2 (2.2)	1.6 (0.9)	6.4 (2.0)	0.002
All patients (N = 60)	7.4 (1.6)	2.6 (2.1)	4.8 (2.3)	<0.001
Neck Disability Index	51.1 (11.1)	45.8 (17.6)		0.037
Zung Depression Index	47.3 (14.5)	34.8 (8.9)		0.027

NRS, numerical rating scale; SD, standard deviation.



**Figure 2.** Analgesic use was applicable for 35/60 patients; 29 of these patients reduced their analgesic use.



**Figure 3.** Patient satisfaction. Fifty of the 60 patients were satisfied with their outcome following occipital nerve stimulation.

**DISCUSSION**

ONS is emerging as a promising treatment modality for medically intractable primary and secondary headache disorders. The results from this study support many smaller cohort published findings (13,24,28,30), further instilling a role for PNFS in the treatment of chronic headache disorders. Here, an average reduction of  $4.8 \pm 2.3$  pain scale points was observed at a mean follow up of  $12.9 \pm 9.4$  months (range 3–42 months) postimplantation. Forty-one of the 60 patients (68%) reported >50% pain relief from intractable headaches, with just more than half of these patients (23 patients) report-

**Table 2.** Complications.

Complication	Outcome Reposition/ Reimplant/ Replace	Explant
Hardware erosion	6	1
Lead/IPG infection	1	3
Leads too tight	1	0
Hardware migration	1	0
Hardware failure	1	0

IPG, implanted pulse generator.

ing improvements of >75%. Similar results have been observed in a recent randomized, multicenter, double-blinded study where 66% of patients at the one year follow-up reported good to excellent pain relief following occipital nerve PNFS (29).

Improvements in pain relief were found to inversely correlate with reductions in medication use, with 82% of patients taking prophylactic and/or symptom-related analgesics reporting reductions following PNFS. Comparable results have been observed in a prospective pilot study where ten of 11 patients with C2-mediated occipital headaches reported medication reductions and substantial improvements in function following PNFS (5). Given the disabling nature of this condition and the ensuing economic burden for both the patient and society, the NDI was used in this present study to measure alterations in disability and function following PNFS for a range of life factors. These factors included severity of headaches, the ability to concentrate, drive, read, and perform personal care duties, along with quality of sleep and recreation time. Patients reported a reducing trend in the level of disability and improved functional ability following PNFS.

As with all medical interventions, there often remains a cohort of nonresponders. In our study, we found that ten patients were either not completely satisfied or were unsatisfied with their treatment outcome. Not surprisingly, these patients also reported fair to poor pain relief, and if applicable, no changes to their medication use despite having initially undergone a positive trial period of the PNFS device. Unfortunately, there appears to be no fool-proof predictors of PNFS efficacy. To date, a positive trial period is deemed to be the most likely indicator, with occipital nerve blocks shown to be unsuccessful in predicting ONS efficacy (31). A recent retrospective series has associated medication overuse with a less favorable ONS

outcome in migraine patients (32). However, it remains to be prospectively studied whether medication overuse is a predictor of negative outcomes. At present, weaning patients off excessive medication use is suggested prior to implantation as it may improve the patient's condition for a large part by itself.

The rate of surgical revisions for PNFS in the head region is often higher than torso lead placement. We observed 14 complications in our cohort of 60, with hardware erosion occurring in half of the 14 cases. Importantly to note, only one of these hardware erosion patients required explant of their PNFS systems, with the remaining six cases rectified with surgical revisions, replacements, or repositions. In the literature, lead erosion and migration tend to be the most common cause of surgical revision. A study by Schwedt and colleagues on 15 patients described an increasing lead migration rate with time of 33% at six months to stunning 100% of cases by three years (33). However, other reports have described a more modest long-term complication rate, such as Slavin et al. (27) where by 35 months postimplantation, three of the total 22 patients underwent repeated operations because of lead erosion, infection, or migration, and further three patients had their systems explanted because of loss of effectiveness (two cases) or late infection (one). In our study, most complications occurred within the first year following implantation, and length of implant time was not found to be a factor in the likelihood for surgical revision. Based on earlier experiences, we considered that placing leads from a central incision had a much higher migration risk. Occipital leads were therefore placed for the side that the IPG would subsequently be implanted. A larger incision was made over the mastoid process for the anchoring to occur, and a small stab incision was made centrally to place the more distal lead, which was then fed back to the major incision via a retrograde Angiocath. A J-shaped needle (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and 2/0 VICRYL™ suture (Ethicon Inc., Somerville, NJ, USA) was used to help anchor directly to the lead through the small incision. Unlike published technical notes (34), we elected not to use anchors in the head because of our earlier experience with erosions. The lead was instead sutured directly. A small undercut flap was made using a finger to allow a redundant loop of lead to be placed; however, it was not turned on itself. The lead was then sutured with further 2/0 Vicryl. Tunneling ensued to the pocket via a zig-zagging type process. We normally would tunnel from the mastoid incision back centrally and then across toward the scapula. In cases where the IPG was placed in over the anterior pectoralis region, the lead would then be tunneled from this lateral position back to the IPG. Alternatively, if the lead was placed in the posterior axillary fold, we would then swing the tunneling tool back out to the lateral axilla. It was our view that these technical refinements helped reduce our lead migration rate in this series. Presently though, the equipment used for PNFS in the craniofacial regions is adapted from conventional spinal cord stimulation, which is seen to add to the inherent technical difficulties and considerations associated with craniofacial lead implantation such as placement, anchoring, IPG location, and the degree of stress relief in the lead.

In this study, no attempt was made to break the headache presentation into specific diagnostic subgroups. We took a pragmatic approach to the presenting problem (headache) as we recognized that headache is predominantly stratified according to symptom congregation rather than pathology, and that some headache presentations are not clearly stratifiable. We consider that future prospective studies should define the diagnosis according to contemporary International Classification of Headaches Disorders protocols.

Furthermore, it would be of interest to know for each diagnostic entity treated with PNFS the likelihood of success, the most useful initial implantation site (e.g. just ONS or ONS plus facial stimulation), and the best stimulation parameters.

Although this case series along with others describes the usefulness of PNFS in treating medically intractable head pain, it is vital that further investigations be carried out to clarify the ideal neurostimulation responder and possibly predict outcomes. Robust clinical trials along with insightful discussions on the means of overcoming the placebo issue plaguing neurostimulation are strongly needed in the ever-evolving field of neuromodulation.

## CONCLUSION

Given the reversible and safe nature of this modality, along with the consistently positive results found in the literature, implantation of a PNFS system in the craniofacial region should be offered to patients with frequent, intense, and impairing chronic headaches who have failed reasonable conservative and interventional therapies. Improvements in patient selection, equipment technology, and refinement of implant techniques may make this effective treatment an even more promising pain relief strategy for an otherwise intractable condition.

## Authorship Statement

Drs. Verrills, Mitchell, and Vivian conducted the study, including patient recruitment. They also reviewed and edited the manuscript. Ms. Rose and Dr. Barnard collected, analyzed the data, and wrote/edited the manuscript.

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