Efficacy of Electroacupuncture for the Treatment of Postherpetic Neuralgia: Study Protocol for a Multicenter Randomized Controlled Trial

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Introduction: Postherpetic neuralgia (PHN) is a severe complication of herpes zoster (HZ), representing an important burden of disease in the elderly. Electroacupuncture (EA) has become growingly appreciated as a therapy of PHN with the situation that effectiveness of conventional therapy of PHN is less than ideal. Owing to its low price, no side effects, high safety and high patients acceptance, EA has been used in treating PHN more frequently. Therefore, the randomized controlled trial which is to evaluate the effectiveness and safety of EA in patients with PHN and whether EA could be an alternative therapy of medication is needed.

Patients and Methods: A total of 88 patients with PHN will be recruited from 2 hospitals and randomized assigned to EA group or Medication group in a 1:1 ratio, utilizing a central randomization system. The trial will involve a 4-week treatment period, and a 4-week follow-up period. All variables will be evaluated at week 0 (baseline), week 2 (treatment), week 4 (treatment), week 8 (follow-up) and week 16 (follow-up). Primary outcomes will be pain intensity. Secondary outcomes will contain quality of life, mood state and sleep quality. All adverse effects will be assessed during the trial.

Conclusion: This study will provide significant evidence that whether EA therapy is effective and safe for patients with PHN and whether EA could be an alternative therapy of medication.

Ethics and Dissemination: Ethics approval has been obtained from the Ethics Committee of the Hangzhou Third People’s Hospital (No. 2021KAO43). Informed consent will be signed before enrolment. Results of this trial will be presented to international journals for publication and be reported in relevant international conferences.

Trial Registration Number: This protocol has been registered in the Chinese Clinical Trial registry with the identification code ChiCTR2100054592.

Keywords: postherpetic neuralgia, electroacupuncture, pain, randomized controlled trial, protocol

Introduction
Postherpetic neuralgia (PHN) is a condition which results from nerve dysfunction following an episode of acute herpes zoster (AHZ) previously and is the most frequent and refractory sequela of AHZ. PHN can occur in 20% of patients at any age, whereas, people over 50 are more prone to developing PHN.\textsuperscript{1} Hence, most patients in a condition of PHN always take on more medications pertaining to other age-related issues that result in synergistic side effects when they add PHN pharmaceuticals, which leads to a less pain relief.\textsuperscript{2} Except increasing age, low immunity is a risk factor as well. Approximately 2% patients with AHZ may be evolved into a chronic pain syndrome and persist for 5 years or more,\textsuperscript{3} which may lead to a reduced quality of life and sleep of the afflicted. Patients with PHN generally has a longer duration,
contributing to financial burdens on individuals and society, and describe different types of pain: a persistent deep aching, a burning pain, allodynia as well as itching which could be more irritating than the pain itself as many patients complain.\textsuperscript{2}

At present, oral drug shows acceptable analgesia for PHN prevalently, for instance, Gabapentin and Pregabalin are the most commonly used first-line therapies for chronic PHN pain both approved by Food and Drug Administration (FDA) for the PHN management, furthermore, topical therapy, such as lidocaine 5% patch and the capsaicin 8% patch is also an effective method available for PHN.\textsuperscript{4,5} Whereas, this benefit usually comes with a cost- serious side effect and drug dependence to the human body, Besides the side effects, the effectiveness of pharmaceutical and surgical treatments for PHN is hardly satisfactory,\textsuperscript{2,6} thus it is still insufficient for chronic pain.\textsuperscript{7} Up to now, although the vaccine can prevent PHN cases and lower the incidence of PHN in part,\textsuperscript{8} we still lack a disease-modifying therapy.

Acupuncture, originated in ancient China, is a noninvasive treatment, and according to a variety of increasingly empirical and clinical evidences, has been shown to be an economical, effective, safe, and non-side-effect-causing therapy, used in various chronic pain,\textsuperscript{9–11} containing PHN.\textsuperscript{12–14} Based on our studies conducted previously,\textsuperscript{15–19} acupuncture, especially electroacupuncture (EA), has been found to be effective for alleviating neuropathic pain. The exact mechanism underlying EA analgesia is complex and remains unclear. Some researches reveal that EA analgesia associates with bioactive chemicals, such as opioids, serotonin, norepinephrine through peripheral, spinal, and supraspinal systems.\textsuperscript{11} In line with existing animal experiments, 2Hz EA shows more successful analgesia for chronic pain models of neuropathic pain,\textsuperscript{20–22} comparing with 100Hz. Furthermore, Combined with previous trials of our team that 2Hz EA was better than 2/100Hz EA in maintaining analgesic effects for Trigeminal neuralgia, EA at 2Hz are supposed to be a more effective frequency for chronic and neuropathic pain. Whereas, the efficacy of EA is not fully accepted worldwide up to now. Despite a number of researches suggesting its effectiveness and widespread use in clinical practice, the current evidence supporting is not strong.\textsuperscript{23,24} Thus, it is necessary to conduct a Randomized controlled trial (RCT) to obtain stronger and valid proof of EA and confirm the effectiveness and safety of EA compared with medication.

**Methods**

**Study Design**

This trial is a multicenter and randomized controlled design. Patients with a prior PHN diagnosis are diagnosed by the research doctors at the outpatient clinics and on the wards will be invited to participate in this trial. After enrollment, eligible participants will be divided into electroacupuncture (EA) group and medication group respectively in a 1:1 allocation ratio through a central randomized system. All participants will receive 4-week treatment and 12-week follow-up, and before entering, they will be asked to sign an informed consent. The trial design is summarized in Figure 1. This trial is aimed at evaluating the effectiveness and safety of electroacupuncture therapy compared with medication. The protocol is based on the standard for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)\textsuperscript{25} and used the SPIRIT reporting guidelines.\textsuperscript{26}

**Participants Enrollment**

Two centers contain the Hangzhou Third People’s Hospital and The Third Affiliated Hospital of Zhejiang Chinese Medical University. Participants will be recruited by means of local newspaper, programs, advertisement in communities and hospitals. Our researchers will screen patients who are interested in this trial through the following criteria, and after signing informed consent, eligible participants will be randomized into two groups with different treatments.

**Inclusion Criteria**

Participants will be included if they (1) meet the diagnostic criteria for PHN\textsuperscript{27}; and (2) have a HZ history, and the duration persists for more than 90 days; and (3) have a Visual Analogue Scale (VAS) not lower than 4; and (4) are 18–80 years old; and (5) sign the written informed consent and can fully understand the protocol.
Figure 1 Flow chart of the study process.

Abbreviations: EA, electroacupuncture; VAS visual analogue scale; MOS-SS the Medical Outcomes Study-Sleep Scale; SF-MPQ Short-Form of McGill Pain Questionnaire; BPI-SF Brief Pain Inventory; HAMA Hamilton Anxiety Scale; HAMD Hamilton Depression Scale; SF-36, Short Form 36 Health Survey.
Exclusion Criteria
Participants will be excluded if they (1) do not meet the inclusion criteria; and (2) suffer from Herpes Zoster which occurs in the head and perineum or which is regarded as the special type of Herpes Zoster; and (3) are pregnant or nursing; and (4) have severe heart diseases, liver, kidney and other organ damages or have other serious skin diseases; and (5) have a cardiac pacemaker; and (6) have intolerance, uncooperative behavior to the study, and the inability to finish the self-evaluation questionnaires; and (7) have participated in other clinical trials in the last 3 months.

Discontinuation Criteria
Participants will discontinue this trial if they (1) have so serious adverse reactions during the study that it is impossible to continue; and (2) have disease progression or severe complications during the trial and need some urgent emergency measures; and (3) have poor compliance or ask to leave the trial halfway.

The physician will evaluate the severity of the situation and discontinue the trial.

Elimination Criteria
Participants will be eliminated if they (1) are not standards-compliant but they are wrongly recruited; and (2) fail to complete the prescribed treatment or data collection due to various reasons and affects the evaluation of efficacy and safety; and (3) leave this trial by themselves; and (4) receive other treatment rather than our intervention.

Randomization and Blinding
This trial is randomized and allocated by a Dynamic Randomization Method of Central Stochastic System. After enrollment, randomization will be performed by an independent researcher who will not be involved in treatment and statistical analyses. The randomization scheme, which allows no one except the top system administrator to view, will be generated by an independent person not involved in this trial. Therefore, the variability of variables such as age and gender will be reduced to a minimum. All assessors, data recorder and statistical analysts will be blinded to assignment and corresponding intervention. Nonetheless, acupuncture manipulators and participants will not be blinded considering the peculiarity of acupuncture. All staff of this trial will perform independently in case of the information exchange about this trial.

Intervention
Participants will receive either EA or medication. Duration of treatment in both groups is 4 weeks with a follow-up period of 12 weeks.

Medication Group
Participants allocated to medication group shall receive oral 150-mg Pregabalin capsules (Produced by Pfizer Pharmaceutical Co., Ltd) twice daily (total daily dose,300mg) for 4 weeks.

EA Group
Participants in EA groups receiving EA treatment of deep needling on planned acupoints use disposable stainless steel needles with a specification of 0.25 mm×45mm and 0.18 mm×25mm (Suzhou Medical Products Factory Co., Ltd, China). The acupoints prescriptions for all are as follow: Ashi acupoints, Shenting (DU24), Baihui (DU20), Sishencong (EX-HN1),and Jiaji acupoints (EX-B2), Hegu (LI4), Waiguan (TE5), Yanglingquan (GB34), Qixu (GB40) on the affected side. Besides, specific needles are connected to EA apparatus and the frequency of electrical stimulation is 2 Hz. The locations of acupoints chosen in this trial are displayed in Table 1.

Every participant will be asked to be settled in a lateral position so that the pain region can be exposed fully. After routine disinfection, needles with a specification of 0.25 mm×40mm will be inserted to a depth of 25 to 40 mm vertically and unilaterally on EX-B2, LI4,TE5,GB34 and GB40 on the affected side. EX-B2 on the ipsilateral side will be selected according to the corresponding ganglia involved by herpes zoster. Ashi acupoints related to the lesion area will be selected (every 2-to-3-cm interval of the painful region of PHN is used as an acupoint) and needles with a specification of 0.25 mm×40mm will spur the direction of the center of the lesion at 30° on Ashi acupoints. Needles
with a specification of 0.18 mm×25mm will also be used to spur the direction of the center of the lesion at 15° on DU24, DU20 and EX-HN. Then, needles at EX-B2 and Ashi acupoints are connected to EA apparatus respectively. The treatment will last for 30 minutes. The frequency of electrical stimulation will be set as 2 Hz and the stimulation intensity should be increased gradually and to the scope that participants can be tolerant.

In addition, if the neuropathic pain cannot be endured during the trial, Acetaminophen orally will be allowed as the rescue analgesia but instructed not to exceed 3 grams per day and all therapies ought to be carefully recorded in detail on CRF in time.

All treatment will be operated by doctors who have at least 3-year clinical experience in acupuncture. Participants will cooperate with the treatment 3 times a week for 4 weeks continuously, moreover, any other treatment which may affect the trial will be prohibited. The adverse events will be reported, handled and recorded in a timely manner.

Outcome Measures
Participants suffering from PHN are always troubled with chronic pain, insomnia, and emotional handicap. Therefore, we chose related outcomes to evaluate their mental and physical condition in the trial.

Participants in both two groups will be evaluated at week 0 (baseline), week 2 (treatment), week 4 (treatment) week, week 8 (follow-up), and week 16 (follow-up), assessors to evaluate the changes of pain intensity, insomnia severity, emotional status and life quality. Moreover, assessors will monitor reasons for participants discontinuing trial during the treatment period as well as adverse reactions at each treatment session to evaluate the security of the therapies.

The schedule of this trial is presented in Table 2.

Primary Outcome Measure
Primary outcome measures is Visual Analogue Scale (VAS) which ranges from 0 (no pain) to 10 (The worst unbearable pain) and is chosen to assess merely pain severity. Due to its simplicity and objectivity, VAS is widely used in clinical study.

Table 1 Location and Indication of Acupoints for Treating PHN

| Acupoints     | Location                                      |
|---------------|-----------------------------------------------|
| Primary acupoints                                      |
| (1) Ashi acupoints                                     |
| (2) Jiaji acupoints (EX-B2)                            |
| (3) scalp acupoints                                    |
| Shenting (DU24)                                        |
| Baihui (DU20)                                          |
| Sishencong (EX-HN1)                                    |
| Supplementary acupoints                                |
| Hegu (LI4)                                             |
| Waiguan (TE5)                                          |
| Yanglingquan (GB34)                                    |
| Qiuxu (GB40)                                           |

Table 1: Location and Indication of Acupoints for Treating PHN.

Primary acupoints
(1) Ashi acupoints Ashi points are defined as the most painful points in the herpes zoster lesion are
(2) Jiaji acupoints (EX-B2) Jiaji acupoints on the ipsilateral side will be selected according to the corresponding ganglia involved by herpes zoster. Jiaji acupoints (EX-B2) are located 0.5 cun bilateral to the posterior midline in the dorsal thoracic and lumbar region, ranging from the first thoracic vertebra to the fifth lumbar vertebra.
(3) scalp acupoints
Shenting (DU24) Shenting is on the midline of the head, 0.5 cun directly above the midpoint of the posterior hairline.
Baihui (DU20) Baihui is on the midline of the head, 7 cun directly above the midpoint of the posterior hairline.
Sishencong (EX-HN1) Sishencong is on the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.
Supplementary acupoints
Hegu (LI4) Hegu is Between the 1st and 2nd metacarpal bone, and in the midpoint of the radial side of the 2nd metacarpal bone; or, the transverse crease of interphalangeal joint of one thumb are placed on the stretched hukou between the thumb and index finger of the other hand, and the acupoint is where the tip of the thumb touches.
Waiguan (TE5) Waiguan is on the line joining Yangchi and the tip of elbow, 2 cun above the dorsocarpal transverse crease, between the ulna and radius.
Yanglingquan (GB34) Yanglingquan is in the depression anteroinferior to the head of the fibula.
Qiuxu (GB40) Qiuxu is anterior and inferior to the lateral malleolus, in the lateral depression of the extensor digitorum longus tendon.
Secondary Outcome Measure

Secondary outcome measures contain Short-Form of McGill Pain Questionnaire (SF-MPQ), Brief Pain Inventory (BPI-SF), the Medical Outcomes Study-Sleep Scale (MOS-SS), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Short Form-36 Health Survey (SF-36). SF-MPQ focuses on characteristics, intensity, applying syndromes of pain as well as their change during the treatment, besides, it does not spend too much time, so it could be sensitive to clinical change and reflect the effectiveness of the therapy. BPI-SF includes descriptive words such as the cause of pain, the nature of pain, the impact on life and the location of pain, and is used to describe the degree of pain and evaluate the pain in many aspects. MOS-SS consists of 12 items related to the sleep quality within a 4-week recall period. Participants with PHN are usually beset by imaginative chronic pain, thus emotion status will affect their pain intensity conversely, thus HAMA and HAMD will be adopted to assess mental condition of participants, containing anxiety and depression respectively. SF-36 is a questionnaire that has been clarified to have reliability and validity and is used widely to evaluate people’s quality of life.

Informed Consent and Ethic

Before inclusion, all participants will be fully aware of this trial in detail including benefits and risks, and asked to sign the informed consent. Moreover, they will be informed of that it’s free to participate in this trial and they can withdraw

Table 2 Schedule of Enrolment, Treatments, and Assessments

| Study Period | Enrolment/ Baseline | Treatment (Weeks) | Follow-Up (Months) |
|--------------|---------------------|-------------------|-------------------|
| Assessment Point | | | |
| Time | –2 Weeks to 0 | 2 Weeks ± 3 Days | 4 Weeks ± 3 Days | 8 Weeks ± 3 Days | 16 Weeks ± 3 Days |
| Eligibility screening | * | | | | |
| Demographic data | * | | | | |
| Case data | * | | | | |
| Inclusion criteria | * | | | | |
| Exclusion criteria | * | | | | |
| Discontinuation criteria | * | | | | |
| Elimination criteria | * | | | | |
| Informed consent | * | | | | |
| Treatment | * | * | | | |

Outcome Assessment

(1) VAS | * | * | * | * | *
(2) MOS-SS | * | * | * | * | *
(3) SF-MPQ | * | * | * | * | *
(4) BPI | * | * | * | * | *
(5) HAMA | * | * | * | * | *
(6) HAMD | * | * | * | * | *
(7) SF-36 | * | * | * | * | *
Safety assessment (EA) | * | | | | |
Safety assessment (Medication) | * | | | | |
Compliance assessment | * | | | | |
Other treatment | * | | | | |
Adverse events | * | | | | |
Data processing | * | | | | |
Investigator qualification review | * | | | | |

Abbreviations: VAS, visual analogue scale; MOS-SS, the Medical Outcomes Study-Sleep Scale; SF-MPQ, Short-Form of McGill Pain Questionnaire; BPI-SF, Brief Pain Inventory; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; SF-36, Short Form 36 Heal.
after participating at their own will without any reason at any time. It’s a patient’s prerogative to decide whether to participate in this trial or not. All information related to participants will be kept confidential.

This trial has obtained ethics approvals from Hangzhou Third People’s Hospital (No. 2021KAO43).

**Study Registration**
This trial was registered in the Chinese Clinical Trial Registry (ChiCTR2100054592).

**Quality Control**
For the sake of minimizing treatment bias, two centers will designate one professional acupuncture doctor respectively who has at least 4-year experience of acupuncture to receive intensive training based on the treatment procedure of this trial. Simultaneously, data assessors will be trained together, and practice to collect outcome assessments and fill in case report forms normatively. Data related to this trial will be recorded in case report forms and there will be a specific person in charge of entering those raw data in every center. Considering the bias minimization, except acupuncture doctors and participants, clinical research coordinators (CRCs)(including outcome assessors, data recorders, data entry clerks and statistical analysts) will be blinded to assignment. All staff in two centers will meet every 3 months to talk over emerging issues and corresponding solutions during our trial.

To enhance the adherence of participants and avoid attrition bias induced by the dropout and loss to follow up, all of them will obtain 100 RMB per person transport allowance.

**Safety Evaluation**
Researchers will record adverse events caused by EA and Pregabalin during treatment in detail (time, degree, duration and solution), containing severe pain, bleeding, skin pigmentation, fainting, sweating, dizziness (acupuncture related), and gastrointestinal discomfort, drug allergies (medication related). At the end of the trial, researchers will calculate the frequency of adverse events arisen. If encountering extremely severe adverse events, researchers should keep ethics committee advised of this immediately, who will determine whether the participant should be withdrawn from the trial.

**Sample Size**
Sample size is calculated by PASS software (version 15.0.5, NCSS, LLC). The primary outcome is VAS, and based on the literature, the effective rate of Pregabalin is 60%, meanwhile, according to our early trials, the effective rate of 2 Hz EA is 92.3%, with the following assumptions: α of 0.05 (two-tailed), power of 90%, and a 1:1 ratio, at least 35 participants in each group will be obtained. Accounting for a possible dropout rate of 20%, each group should include no fewer than 44 participants and there will be at least 88 participants included in this trial. The following formula was used:

\[
N = \frac{2[Z_{\alpha/2}\sqrt{2pq} + Z_{\beta}\sqrt{pq_0q_1 + p_1q_1}]}{(p_0 - p_1)^2}
\]

**Statistical Analysis**
The data will be performed by SPSS 19.0. Data will be expressed as mean ± standard deviation (x̅ ± s) and percentage. Continuous data in normal distribution will be examined by analysis of variance and t-test with Dunnett’s adjustment for multiple comparisons, and categorical data will be examined by Chi-square test. Difference is considered statistically significant at P < 0.05. Besides, all the data will be analyzed using both ITT and PP datasets to reduce deviation.

**Discussion**
PHN representing a major health problem is the most intractable complication of HZ, and is a complex neuropathy with regarded of peripheral nerve system. Pharmaceutical therapy, including systemic therapy generally with anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants and topical therapy (lidocaine or capsaicin) has long been regarded as the primary option for PHN, mostly affecting the elderly who has a lower immunity. Electroacupuncture, as
a non-pharmaceutical therapy, is recognized as a strikingly effective analgesic means against various types of pain,\textsuperscript{32–34} which bases on traditional acupuncture combined with electrical stimulation. The mechanism of its analgesia involving peripheral and central nerve system has been poorly identified. As is reported, researches\textsuperscript{34–37} reveal that EA exerts inhibitory effect on pain via the interaction and integration between acupuncture signals and pain signals at different levels of the nervous system, with plenty of bioactive substances participating in, such as serotonin,\textsuperscript{38,39} \textgamma-aminobutyric acid (GABA),\textsuperscript{40} opioid peptide,\textsuperscript{41} TRPV1 and P2X3,\textsuperscript{42,43} and so on.\textsuperscript{44} Although various clinical experience and previous studies demonstrate that\textsuperscript{14,45–47} acupuncture will alleviate the intensity of pain in PHN patients and concomitant clinical symptoms of PHN, like insomnia, depression, anxiety, and low quality of life, most exiting trials exhibited poor methodological quality and evidence.\textsuperscript{12,48,49}

Thus, this RCT with rigorous methodological quality is urgently needed to further investigate the effectiveness and safety of EA for PHN and explore whether 2 Hz EA can serve as an alternative therapy of Pregabalin or not. First, we choose SF-MPQ, BPI-SF, MOS-SS, HAMD, HAMA, and SF-36 as outcome measures for PHN participants whose chronic pain of high intensity could disturb their daily life,\textsuperscript{30} encompassing 4 aspects involving pain, sleep quality, emotion and life quality, which will enable a better overview of participants’ general status comprehensively and systematically. Second, with numerous studies having proved the curative effectiveness of acupuncture for PHN,\textsuperscript{12,13,47,50,51} our trial will utilize a fixed acupuncture regimen consisted of Jiaji acupoints (EX-B2), local Ashi acupuncture, distal acupuncture on the affected side (LI4, TE5, GB34, GB40) and scalp acupoints (DU24, DU20, EX-HN1). Jiaji acupunctures are located on both sides of the spinal column, 0.5 cun lateral to the lower border of each spinous process, stimulations on which could inhibit the expression of proinflammatory cytokines and Nogo-NgR signal pathway to facilitate nerve growth,\textsuperscript{52} and awake the cutaneous-visceral reflexes to regulate related nerve and organs.\textsuperscript{53} It has been reported that\textsuperscript{54} scalp acupuncture has a targeted stimulation for cerebral cortex function areas that ordinary acupuncture does not have, and could facilitate the balance of physiological functions of the cerebral cortex and regulate the autonomic nervous system, thus scalp acupuncture has more advantages in the treatment of neurological diseases. According to one literature,\textsuperscript{55} scalp acupuncture plus conventional acupuncture could reduce depressive symptoms significantly which were regarded as the most effective approach for treating Post-stroke depression (PSD) in the 12 types of acupuncture treatment. So scalp acupuncture will be utilized to promote participants’ psychological condition in this trial. Third, as is reported,\textsuperscript{56} EA analgesia at different frequency was mediated through different endogenous opioid pathways in rats. Moreover, 2 Hz had a better effect on spared nerve injury (SNI) model,\textsuperscript{57} and in a rat trial,\textsuperscript{58} researchers observed that stimulation at 2 Hz or 100 Hz both had a reduction of post-incision hyperalgesia, whereas 2 Hz EA last longer, whose finding is similar with our advance trial’s that 2 Hz EA has a better long-lasting analgesic effect. Therefore, we choose 2 Hz as the final frequency.

**Conclusion**

In conclusion, it’s a study protocol of a multicenter, assessor-blinded, randomized, controlled trial, whose purpose is to explore the effectiveness and safety of EA, compared to medication and whether EA could be an alternative modality of medication for patients with PHN. The research results will prove whether EA could mitigate pain intensity, improve sleep quality and emotion condition. This finding will be a meaningful evidence in clinical practice for treating PHN, and will provide a therapy with fewer side effects for patients with PHN.

**Ethics Statement**

This trial was approved by the Hangzhou Third People’s Hospital (No. 2021KAO43) and the Third Affiliated Hospital of Zhejiang Chinese Medical University. And this trial will be conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Before enrollment, all individuals in this trial will be asked to write a informed consent. Written informed consent will be obtained from the participants for the publication of this trial and any accompanying images.

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Author Contributions
All authors have made a significant contribution to the manuscript, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. And they will also accept the responsibility for the study protocol.

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Disclosure
The authors report no conflicts of interest in this work.

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