BMJ Open

Effectiveness of transcranial direct current stimulation (tDCS) as adjunctive treatment for chronic headache in adults with clinically stable systemic lupus erythematosus (SHADE): a randomised double-blind multiarm sham controlled clinical trial

Riwanti Estiasari ,[1,2] Amanda Tiksnadi,[1,2] Dyah Tunjungsari,[1,2] Kartika Maharani,[1,2] Tiara Aninditha,[1,2] Henry Riyanto Sofyan,[1,2] Irma Savitri,[1,2] David Pangeran,[1,2] Ivan Jeremia,[1] Alvina Widhani ,[2,3] Anna Ariane[2,4]

To cite: Estiasari R, Tiksnadi A, Tunjungsari D, *et al*. Effectiveness of transcranial direct current stimulation (tDCS) as adjunctive treatment for chronic headache in adults with clinically stable systemic lupus erythematosus (SHADE): a randomised double-blind multiarm sham controlled clinical trial. *BMJ Open* 2023;**13**:e076713. doi:10.1136/bmjopen-2023-076713

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-076713).

Received 14 June 2023
Accepted 30 November 2023

For numbered affiliations see end of article.

Correspondence to
Dr Riwanti Estiasari;
riwanti.estiasari04@ui.ac.id

ABSTRACT

Background Chronic headache is a 'silent' neuropsychiatric systemic lupus erythematosus symptom with heterogeneous prevalence, potentially reaching 54.4%. It may reduce quality of life by increasing the likelihood of depression and sleep disturbance. While pharmacotherapy remains the first-line treatment, the current management is still challenging and needs other non-invasive modalities. An effective, tolerable and disease-specific treatment modality including transcranial direct current stimulation (tDCS) is considered to reduce the frequency of chronic headaches, including in SLE. Until recently, there was no standard protocol for tDCS in treating headaches.

Methods and analysis SHADE is a single-centre randomised double-blind multiarm sham-controlled trial for adults with clinically stable SLE, chronic headaches and without history of traumatic brain injury, brain infection, stroke or brain tumour. Random allocation is conducted to 88 subjects into 3 treatment groups (administration at primary motor, primary sensory and dorsolateral prefrontal cortex) and control group in 1:1:1:1 ratio. The primary endpoint is reduced number of headache days after adjunctive tDCS. The secondary endpoints are reduced headache intensity, increased quality of life, increased sleep quality, decreased depression and reduced analgesics use. The outcome is measured monthly until 3-month postintervention using headache diary, 36-Item Short Form Survey, Chronic Headache Quality of Life Questionnaire, Pittsburgh Sleep Quality Index and Mini International Neuropsychiatry Interview version 10 (MINI ICD 10). Intention-to-treat analysis will be performed to determine the best tDCS electrode placement.

Ethics and dissemination Ethical approval had been obtained from the local Institutional Review Board of Faculty of Medicine Universitas Indonesia. Results will be published through scientific relevant peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The effectiveness of transcranial direct current stimulation (tDCS) as adjunctive treatment for chronic headache in adults with clinically stable systemic lupus erythematosus (SHADE) is the first randomised controlled trial comparing three different electrode placement protocol and a sham of tDCS for managing chronic headache in patients with SLE.
⇒ Screening will be performed for 4 weeks to ensure that the subjects fulfil the criteria of chronic headache. Headache is documented using the gold standard of headache monitoring, headache diary.
⇒ The outcomes of this study are not only the number of headache days and headache intensity but also quality of life, depression and sleep quality.
⇒ Long duration of observation, risk of flare-up and complications of the subjects could present significant threats of drop-out during the study.

Trial registration number NCT05613582.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that can affect both the central and peripheral nervous systems in about 30% of cases. Chronic headache in SLE is 1 of 19 symptoms of neuropsychiatric SLE based on American College of Rheumatology (ACR) criteria.[1] In SLE, chronic headaches are frequently observed, and they may lower quality of life, leading to significant comorbidities, such as depression and anxiety, which are causes of disability.[1 2]

Chronic headache is typically described as headaches on 15 or more monthly for at least 3 months. In contrast to episodic headaches, chronic headaches tend to be less receptive to acute treatments. Chronic headache consists of both chronic primary headache (eg, chronic migraine), chronic secondary headache (eg, chronic cervicogenic headache and chronic neuropathic headache and facial pain (chronic trigeminal neuralgia).[3]

The pathophysiology of chronic headache, especially the migraine type, is the activation of trigeminovascular system as a peripheral nervous system circuit. The cerebral cortex of patients with chronic headaches was found to be more hypersensitive to external stimuli. In addition, there were dysfunction and changes in the functional connectivity of the subcortical pathways (thalamocortical dysrhythmia).[4 5]

Chronic headaches are also associated with sleep disturbances. Recent biochemical and functional imaging studies have identified the involvement of diencephalon and brainstem as well as dysregulation of the sleep-wake cycle, orexins, melatonin, pituitary polypeptide adenylate cyclase, serotonin, dopamine and adenosine in the pathophysiology of migraine.[6]

Management of chronic headaches in SLE is still a challenge, current medical therapies can cause side effects and complications, especially in long-term use. Along with advances in technology and information regarding the involvement of cortical and subcortical pathways in the process of chronic pain, the use of other non-invasive and direct modalities of cortical and subcortical pathways as adjuvant therapy in the management of chronic headache is urgently needed.[7–10]

Transcranial direct current stimulation (tDCS) is a technique that uses DC electric currents to directly modulate the polarisation and action potentials of neurons in the brain. In clinical practice, tDCS has clinical effectiveness in the prevention and management of chronic pain including headaches. It is quite easy to be used, relatively inexpensive and safe, which results in tDCS as a promising option.[11 12]

The use of tDCS in treating headache in several studies has shown good results. A meta-analysis studies showed that 4 weeks of tDCS was effective in reducing the intensity and duration of migraine episodes, which lasts up to 4–12 weeks after stimulation.[13]

Until now, there was no standard protocol for using tDCS in treating headaches. Coactivation of the primary sensory cortex (S1), primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) in processing and interpreting pain has become the basis for several studies in determining stimulus targets.[11 12 14–17] Four randomised controlled trials (RCTs) of anodal tDCS stimulation at M1 and two RCTs of anodal stimulation of the left DLPFC were effective in treating migraine and medication overuse headache (MOH). Stimulation of cathodal tDCS in M1 and S1 was also effective for migraine management at 3-month follow-up.[17 18]

The M1 plays a major role in the components of the pain matrix.[19] M1 is also associated with the somatosensory cortex and other brain structures such as the thalamus, hypothalamus and periaqueduct of the substantia nigra, which have their respective roles in the pain interpretation process. Stimulation of tDCS on M1 is expected to modulate pyramidal and extrapyramidal pathways through excitation and inhibition of other structures.[14] Stimulation of anodal tDCS on M1 has shown effectiveness in reducing migraine-type headache intensity, duration of migraine, number of attacks, number of analgesic consumptions and improving quality of life.[11 14]

The modulation of the primary sensory cortex (S1) was selected for its relationship to other cortical and subcortical areas, particularly M1. The primary sensory cortex is part of a multisensory integration system, thus cathodal tDCS stimulation with an inhibitory effect on S1 is expected to reduce synaptic deficits or synaptic lock when multisensory integration occurs in migraine attacks.[18 20]

Stimulation of the DLPFC increases perfusion in specific brain regions, including the insular cortex, cingulate cortex and periaqueductal grey. When connected with the limbic system, this form of stimulation can regulate how inhibiting pain signals perceive chronic pain through the descending fibres of the prefrontal cortex.[21]

Stimulation of anodal tDCS at DLPFC also showed promising headache control. The DLPFC connects to areas of the cortex and subcortex and bridges the circuits involved in cognitive and emotional processes. Stimulation of this area will also modulate the activity of other subcortical structures such as the caudate nucleus and anterior cingulate cortex.[15 16 19]

The effectiveness of tDCS as adjuvant therapy in SLE with chronic headache is currently unknown. This study aims to assess the effectiveness of the tDCS protocol as an adjuvant therapy for reducing chronic headache in SLE. In addition, this study will also provide an effective tDCS protocol for chronic headache in patients with SLE.

Study objectives

The primary objective of this trial is to determine the effectiveness of tDCS as adjuvant therapy in reducing the number of headache days after the stimulation at the primary motor cortex (M1), primary sensory cortex (S1) DLPFC compared with sham (control) in patients with SLE with chronic headache who received standard therapy.

The secondary objectives are: (1) to compare the effectiveness of tDCS as adjuvant therapy with stimulation in the M1 cortex, S1 cortex and DLPFC compared with sham (control) in patients with SLE with chronic headache who received standard therapy, using the parameter as follows: headache intensity, quality of life, sleep quality, depression level and analgesic use and (2) to measure the long-term effect of tDCS therapy in patients with SLE with chronic headache.

METHODS AND ANALYSIS

Trial design

This is a protocol of a single-centre double-blind randomised multiarm sham controlled clinical trial at Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. Cipto Mangunkusumo Hospital is a national tertiary referral hospital in a huge metropolitan city in Indonesia that commonly manages SLE. This trial has also been prospectively registered at ClinicalTrials.gov (NCT05613582).

Participants

The inclusion criteria are (1) age ≥18 years old; (2) have been diagnosed with SLE based on 2019 European League Against Rheumatism/ACR classification criteria for SLE (ACR) and (3) fulfilling the diagnostic criteria for chronic headache (occurs in ≥15 days per month for at least 3 months, based on third International Headache Society (IHS) criteria).

The exclusion criteria are (1) in a state of relapse/flare; (2) having allergic reactions/skin infections/wounds/cranial defects/metal implants in the electrode installation; (3) having a history of brain tumour, severe traumatic brain injury or stroke and (4) refusing to participate in the study.

Chronic headache is described as headaches of 15 days/month for at least 3 months, which consists of both chronic primary or secondary headache which was not attributed to structural brain injury including brain tumour, severe traumatic brain injury or stroke. It is suspected by history taking and diagnosed using headache diary by the study doctor, which is verified by a neurologist in the study team. Flare is defined as increased SLE disease activity in ≥1 organ system that results in worsened clinical or laboratory parameters. This condition is determined using SLE disease activity index 2000 and verified by a rheumatologist or immunologist in the study team.

Enrolment will be terminated if the subject experience relapse/flare or have the corticosteroid dose increase of more than 20 mg/day prednisone or its equivalent during intervention until 3 months postintervention; is not comply to therapeutic interventions for more than two times, refuses in completing headache diary, or retracts the informed consent. Study termination will not affect the standard health services that the subject will receive.

While participating in this research, subjects can still participate in another observational research and be approved by the main researcher. However, subjects should not be included in other intervention studies.

Recruitment

Screening will be conducted in the internal medicine clinics with the authority to treat SLE, including rheumatology and allergy-immunology clinic, as well as neurology clinic, which is often being referred to manage headaches. The screening for each subject will be performed for at least 1 month (weeks 0–4, pre-intervention phase) to decide whether the pattern of headache fulfils chronic headache. They will also be screened for other eligibility criteria (preintervention phase). Candidates that are eligible for enrolment will be asked for informed consent by one of the study team and, if consent has been obtained, they will enter the randomisation process. Clinical and physical assessment, headache frequency and severity, quality of life, sleep quality, depression, and analgesics use are also recorded as baseline preintervention data (preintervention phase).

Randomisation

Patients who meet the eligibility criteria will randomly be assigned by a study doctor into four different arms of intervention (sham:M1:S1:DLPFC) with a 1:1:1:1 allocation as per a computer-generated randomisation schedule. Allocation concealment will be ensured until the accomplishment of the study.

Blinding

During the intervention, outcome assessment and analysis phase, the treatment allocation is double blinded to the subjects, their family/caregiver and all study investigators except the one who is in charge of treatment allocation.

Interventions

The intervention phase starts at weeks 4–8 at a frequency of twice a week. Trained study members will perform the intervention. tDCS will be delivered using the direct current (DC) stimulation generated by the battery in the tool (neuroConn DC-stimulator Plus, Germany). The electricity will flow through a cable connected to two rubber electrodes (size 5×7 cm (35 cm^2)). The rubber electrodes will be covered with 0.9% saline solution. The electrode placement on the scalp will follow the international EEG 10/20 system (figure 1).

This study considers tDCS stimulation at M1, S1 and DLPFC due to the report of M1, S1 and DLPFC coactivation in pain processes. Anode stimulation at M1 reduced the migraine intensity, duration, frequency and analgesic use and improved quality of life.[10 16] Another study reported that cathode stimulation at S1 also significantly resulted in managing migraine. The area of DLPFC is connected to cortical and subcortical areas of cognitive

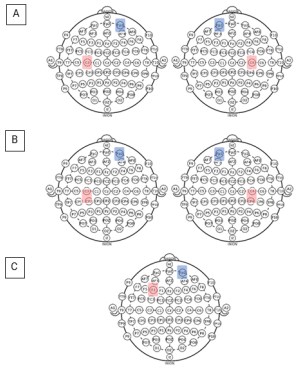

Figure 1 Electrode placement in the (A) M1 experimental group. (B) S1 experimental group. (C) D experimental group.

and emotional processes, which results in better control of headaches.[14 15]

The anode in the M1 experimental group will be placed vertically in the primary motor cortex (C3 or C4) contralateral to the dominant headache side. If there is no predominance on the headache side, the anode is placed in the left primary motor cortex (C3). In the S1 experimental group, the cathode will be applied similarly in the primary sensory cortex (halfway between C3 and CP3 or C4 and CP4). The anode will be placed at F3 regardless of the headache side in experimental group D. The cathode will be placed on the contralateral side of the supraorbital area with the assumption that there is no neuromodulation effect on the subgenual cortex (Fp1 or Fp2). The protocol and electrode placement are illustrated in figure 1.

The treatment intervention programme is 1 mA stimulation for 20 min, twice per week, for 4 weeks. Low-intensity stimulation of 1 mA is chosen due to risk of hypersensitivity in the brain cortex of chronic headache. This stimulation intensity has also been practised and proven safe by Ornello *et al*, Andrade *et al* and Thair *et al* in their study protocol.[18–20] In addition, many studies reported insignificant results between 1 mA and 2 mA stimulation.

The sham intervention procedure is performed to the experimental group, but the device would only conduct an electric current in the first and last 30s of the intervention, which might cause participants to feel a tingling, itchy or burning sensation. All groups will receive an additional 30s ramp-up and 30s ramp-down periods.

Outcome measures

Postintervention assessment will be carried out immediately postintervention (week 8), followed by follow-up at months 1, 2 and 3 postinterventions (weeks 12, 16 and 20, respectively). Clinical, physical, headache and comorbidity parameters are assessed monthly for 3 months (weeks 12, 16 and 20). The timeline and means of assessments are provided in online supplemental file 1. Every subject will have one study doctor to document every variable stated above and perform the follow-up visit to prevent duplicate measurements. Training of study doctors regarding how to fill the instruments is considered unnecessary due to the easy and ready-to-use questionnaire. Communication between study doctors and subjects is maintained professionally to ensure protocol compliance.

Primary outcome

The primary endpoint in this trial is the number of headache days, which is self-reported by the subject using headache diary. Treatment success is defined as decreased number of days with headache at 0, 1, 2 and 3 months postintervention compared with those at preintervention. The number of headache days is defined as total days with at least one headache, which is recorded daily in the headache diary and documented by the study doctor monthly. The consideration of this variable as the primary endpoint is in line with the recommendation in the guidelines of the IHS for clinical trials with neuromodulation devices for the treatment of migraine.[22]

The headache diary is in Indonesian language (see extended data: online supplemental file 2) and consists of headache frequency, severity, characteristics (location and extent of headache, aura), analgesics use, accompanying symptoms (nausea, vomiting, photophobia, phonophobia,), possible triggering factors and the impact to activity daily living. The study doctors will educate the subject to fill the headache diary. It is filled daily and brought to the study doctor to be documented on week 4 (preintervention), 8, 12, 16 and 20 (postintervention months 0, 1, 2 and 3, respectively). Considering that headache is a subjective symptom, self-reported headache diary is the recommended method to understand the headache pattern, avoid recall bias and monitor the change in pattern after intervention. The number of headache days is defined as total days with at least one headache, documented monthly in accordance with the headache diary.

Secondary outcomes

The secondary endpoints in this trial are (1) headache intensity, defined as the most intense headache everyday using Numerical Rating Scale (NRS) and recorded as proportion of no (NRS 0), mild (NRS 1–3), moderate (NRS 4–6) and severe (NRS 7–10) headache; (2) quality of life, recorded numerically using the 36-Item Short Form Survey (SF-36) and Chronic Headache Quality of Life Questionnaire (CHQLQ),[23] (3) sleep quality, recorded numerically using Pittsburgh Sleep Quality Index (PSQI); (4) depression, recorded dichotomously using Mini International Neuropsychiatry Interview version 10 (MINI ICD 10) for depression and (5) use of analgesics.

Headache intensity is defined as the most intense level of headache every day, measured using NRS, and is also self-reported every day in the headache diary. The data will then be classified into no (NRS 0), mild (NRS 1–3), moderate (NRS 4–6) and severe headache (NRS 7–10). Quality of life is measured numerically using SF-36 and CHQLQ, sleep quality is measured numerically using PSQI, depression is documented dichotomously using MINI ICD 10 for depression, and analgesics use is defined by changes in the dose and type of analgesic consumed every week. Higher scores of SF-36 and CHQLQ represent better quality of life whereas higher scores of PSQI represent worse sleep quality. All endpoints are documented and compared between preintervention (week 4) and postintervention (weeks 8, 12, 16 and 20) among intervention groups.

All batteries stated above, apart from analgesics use, are patient-reported outcome questionnaires. NRS, SF-36, PSQI and MINI ICD-10 for depression have been common measures for assessing the headache severity, quality of life, sleep quality and depression among studies, respectively. In addition, SF-36 is also recommended as one of the endpoints to be evaluated

in assessing the benefit of neuromodulation therapy in reducing headache in general. The CHQLQ is a patient-reported headache-related quality of life questionnaire consisting of 14 items, which was scored from 0 to 100 and produces three domains, including role prevention, role restriction and emotional function. This questionnaire is reported to have greater relevance to the patient experience of chronic headache compared with other means of measurement including the Migraine-Specific Questionnaire (V.2.1) and the six-item Headache Impact Test. All batteries of the instrument have been validated in Indonesia.

Treatment success is clinically determined with decreased proportion of headache severity, increased SF-36 score, increased CHQLQ score, decreased PSQI score, decreased proportion of depression and reduced analgesic use at 0, 1, 2 and 3 months postintervention compared with preintervention. Significant statistical association is determined if statistical analysis shows $p<0.05$.

Adverse event monitoring

Subjects who experience side effects of tDCS, including allergies, skin irritation and burns at the electrode pad attachment side, will have the current treatment session discontinued. Minor adverse events or serious adverse event (SAE) without plausible explanation with tDCS will be managed accordingly without unblinding. In addition, minor adverse events will be documented by the study doctors whereas SAEs will also be reported to the local institutional review board (IRB) within 72 hours. Unblinding is performed only if it is deemed necessary, especially regarding patient safety.

External monitoring

The specially assigned monitoring and auditing team are not considered in this trial because tDCS with 1mA stimulation for 20 min is well known to be safe. Study audit and the safety of the trial will be evaluated as needed by the trial team meeting and by the local IRB, respectively.

Data and statistical analysis

Data entry and coding are performed using Research Electronic Data Capture (REDCap) Faculty of Medicine Universitas Indonesia (https://redcap.fk.ui.ac.id/). The data entry is performed by study doctor. While REDcap can only be accessed by those with username and password, all hard copy documents will be stored in a locked place at the study site, which can only be accessed by the study team.

Intention-to-treat analysis will be carried out to compare the efficacy of tDCS before and after intervention, which may further be compared among groups of intervention. Differences in headache frequency, headache intensity, quality of life, sleep quality, depression and analgesics use before and after intervention in the four groups are analysed using repeated measure Multivariate Analysis of Variance (MANOVA). Significance level is set at 0.05. Data analysis will be performed with SPSS V.23.0 and GraphPad software.

Information regarding incomplete clinical data will be traced on medical records or reconfirmed to the subject as appropriate. Any protocol deviation regarding the intervention process or data collection procedure will be documented and considered as limitations of the study. However, inadequate compliance by not following therapeutic interventions for more than two times will be decided as drop-out. Any data from drop-out or protocol deviation subject will still be documented and analysed until the last day of participation.

Patient and public involvement

There was no patient or public involvement.

Sample size

The sample size was estimated using G*Power V.3.1.9.7 with the number of group 4 and number of measurement 4 (8, 12, 16 and 20 weeks). The significance and power are set at 0.05 and 80%, respectively. We use effect size 0.25 (medium effect size for repeated measures MANOVA) and the total sample size n=87, we rounded to 88 and allocated as 1:1:1:1 for sham: M1: M2: DLPFC (22 subjects each group).

Post-trial care

If the tDCS intervention was proven effective, the subjects will be offered to receive the best intervention method at the end of the study.

DISCUSSION

This study is the first experimental trial on the role of tDCS in improving headache outcomes among patients with SLE in Indonesia. The strength of our study is as follows. As a national referral hospital, our patients with SLE presented with many clinical variations across the severity spectrum, which allows us to analyse and manage this heterogeneity, that is, doing subgroup analysis to look for treatment outcome differences across different severity groups. We are also equipped with trained and experienced personnels in neuromodulation, which ensured minimal technical treatment errors when delivering tDCS. Moreover, as described in the Methods section, our outcome (chronic headache) is documented using the gold standard of headache monitoring, headache diary. To our knowledge, our hospital is one of the first hospitals in Indonesia to use headache diary in our routine patient visit.

As headache is a highly multifactorial condition with causes and phenotypes that might overlap with one another, one of our main challenges will be determining whether the headache a patient is a single or multiple entity (eg, 'lupus' headache occurring in a patient with previous existing primary headache). We should also note that patient with chronic headache will most likely be on prophylactic medication, and that will be one of

the factors that should be considered or adjusted when looking at the effect of treatment. MOH is also highly possible in our subjects, and that should be recognised and acknowledged when assessing changes (or its absence) due to treatment effects.

tDCS may become an alternative means to control chronic headaches, as reported in several studies. It has been reported to modulate pain from many aspects of pathophysiology of pain, including the multisensory integration as well as cognitive and emotional pathway. This adjunctive treatment has strengths in the easy application, relatively cheap and non-invasive tools with few side effects. In addition, it can also be administered by trained personnel. While the duration and intensity of tDCS for chronic headache has been studied in a systematic review, the best electrode placement is still not well known.[16 18 20] The findings in this study may serve as knowledge for physicians regarding the effectiveness of tDCS as well as the best electrode placement of tDCS to control chronic headaches in Indonesia, especially in patients with SLE. It may also impact the management of chronic headache in general by including tDCS as an adjuvant and, therefore, reducing the possibility of MOH and improving the quality of life. Although cost-effective measurement is beyond the scope of this study, tDCS is a first-time instrument investment that can be used for multiple patients. Therefore, the use of tDCS may reduce the need of routine headache medication, which is hoped to be cost-effective for the patient and the hospital.

This trial has several potential limitations, including the unadjusted and heterogeneity use of chronic headache medications. This limitation is addressed by analysing medication as a secondary outcome variable. In addition, this study recruited populations from the tertiary hospital in Indonesia. Therefore, it is likely that more severe or refractory chronic headache patients will be recruited. However, as mild-to-moderate chronic headache may be fully controlled with medication, the population in this study may be suitable to assess tDCS as adjunctive treatment for chronic headache.

Ethics and dissemination

Ethical approval had been obtained from the local IRB of Faculty of Medicine Universitas Indonesia (approval number KET-1119/UN2.F1/ETIK/PPM.00.02/2022). This trial has also been registered to ClinicalTrials.gov (registration number NCT05613582). The trial results will be published through scientific relevant peer-reviewed journals. Data requests can be submitted to the corresponding researcher.

Trial status

Recruitment started in January 2023. At the time of submission of this paper, we had recruited 13 participants. It is expected that the report will be completed in January 2025.

Author affiliations
[1]Department of Neurology, Cipto Mangunkusumo National General Hospital, DKI Jakarta, Indonesia
[2]Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
[3]Departement of Internal Medicine Allergy Immunology Division, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[4]Department of Internal Medicine Rheumatology Division, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

Twitter David Pangeran @david.pangeran.vipera@gmail.com

Acknowledgements We thank Komunitas Lupus Sehati for the enthusiastic participation in this study and the healthcare providers in Neurology, Neurorestoration, Rheumatology and Allergy-Immunology clinics of Cipto Mangunkusumo Hospital for the cooperation.

Contributors RE, AT, DT, KM, TA, HRS, IS, IJ, AW and AA were involved in conception and trial design. RE, IS, DP and IJ were involved in drafting of the article. RE and AT was involved in critical revision of the article for important intellectual content. All the authors read, contributed and approved the final version of the article.

Funding This study received a grant from the University of Indonesia, HIBAH PUTI-Q1, Grant Number: NKB-36/UN2.RST/HKP.05.00/2022. The trial funder has no role in the trial protocol design, management, analysis, interpretation and writing of the report.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Riwanti Estiasari http://orcid.org/0000-0003-1982-8716
Alvina Widhani http://orcid.org/0000-0002-1848-6227

REFERENCES

1 Elolemy G, Al Rashidi A, Youssry D, *et al*. Headache in patients with systemic lupus erythematosus: characteristics, brain MRI patterns, and impact. *Egypt Rheumatol Rehabil* 2021;48:31.
2 Vos T, Barber RM, Bell B. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. *Lancet* 2015;386:743–800.
3 Ahmed F, Parthasarathy R, Khalil M. Chronic daily headaches. *Ann Indian Acad Neurol* 2012;15:S40–50.
4 Tu Y, Fu Z, Zeng F, *et al*. Abnormal thalamocortical network dynamics in migraine. *Neurology* 2019;92:e2706–16.
5 Biscetti L, De Vanna G, Cresta E, *et al*. Headache and immunological/autoimmune disorders: a comprehensive review of available epidemiological evidence with insights on potential underlying mechanisms. *J Neuroinflammation* 2021;18:259.
6 Holland PR, Barloese M, Fahrenkrug J. PACAP in hypothalamic regulation of sleep and circadian rhythm: importance for headache. *J Headache Pain* 2018;19:20.

7 John S, Hajj-Ali RA. Headache in autoimmune diseases. *Headache* 2014;54:572–82.
8 Leal Rato M, Bandeira M, Romão VC, *et al*. Neurologic manifestations of the antiphospholipid syndrome — an update. *Curr Neurol Neurosci Rep* 2021;21:41.
9 Shah M, Chaudhari S, McLaughlin TP, *et al*. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. *Clin Ther* 2013;35:486–97.
10 Fregni F, El-Hagrassy MM, Pacheco-Barrios K, *et al*. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. *Int J Neuropsychopharmacol* 2021;24:256–313.
11 Ayache SS, Chalah MA. Transcranial direct current stimulation and migraine—the beginning of a long journey. *J Clin Med* 2020;9:1194.
12 Cai G, Xia Z, Charvet L, *et al*. A systematic review and meta-analysis on the efficacy of repeated transcranial direct current stimulation for migraine. *J Pain Res* 2021;14:1171–83.
13 Vaseghi B, Zoghi M, Jaberzadeh S. How does Anodal transcranial direct current stimulation of the pain neuromatrix affect brain excitability and pain perception? A randomised, double-blind, sham-control study. *PLoS One* 2015;10:e0118340.
14 Mastria G, Viganò A, Corrado A, *et al*. Chronic migraine preventive treatment by prefrontal-occipital transcranial direct current stimulation (tDCS): a proof-of-concept study on the effect of psychiatric comorbidities. *Front Neurol* 2021;12:654900.
15 Lefaucheur J-P, Antal A, Ayache SS, *et al*. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017;128:56–92.
16 Przeklasa-Muszyńska A, Kocot-Kępska M, Dobrogowski J, *et al*. Transcranial direct current stimulation (tDCS) and its influence on analgesics effectiveness in patients suffering from migraine headache. *Pharmacological Reports* 2017;69:714–21.
17 Rahimi MD, Fadardi JS, Saeidi M, *et al*. Effectiveness of cathodal tDCS of the primary motor or sensory cortex in migraine: a randomized controlled trial. *Brain Stimul* 2020;13:675–82.
18 Ornello R, Caponnetto V, Ratti S, *et al*. Which is the best transcranial direct current stimulation protocol for migraine prevention? A systematic review and critical appraisal of randomized controlled trials. *J Headache Pain* 2021;22:144.
19 Thair H, Holloway AL, Newport R, *et al*. Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Front Neurosci* 2017;11:641.
20 Andrade SM, de Brito Aranha REL, de Oliveira EA, *et al*. Transcranial direct current stimulation over the primary motor vs prefrontal cortex in refractory chronic migraine: a pilot randomized controlled trial. *J Neurol Sci* 2017;378:225–32.
21 Wen Y-R, Shi J, Hu Z-Y, *et al*. Is transcranial direct current stimulation beneficial for treating pain, depression, and anxiety symptoms in patients with chronic pain? A systematic review and meta-analysis. *Front Mol Neurosci* 2022;15:1056966.
22 Tassorelli C, Diener H-C, Silberstein SD, *et al*. Guidelines of the International headache society for clinical trials with neuromodulation devices for the treatment of migraine. *Cephalalgia* 2021;41:1135–51.
23 Haywood KL, Achana F, Nichols V, *et al*. Measuring health-related quality of life in chronic headache: a comparative evaluation of the chronic headache quality of life questionnaire and headache impact test (HIT-6). *Cephalalgia* 2021;41:1100–23.