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The safety and feasibility of transcranial direct current stimulation combined with conservative treatment for patients with cervicogenic headaches: A double-blinded randomized control study protocol

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ABSTRACT

Background: Cervicogenic headaches (CGH) are common following concussion and whiplash injuries and significantly reduce patient quality of life. Conservative therapies such as ET (ET) and physiotherapy combined with injection-based therapies are cornerstones of treatment for CGH but have shown limited efficacy. Transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) has shown promise in treating other chronic pain conditions. The primary aim of this trial is to evaluate the feasibility and safety of tDCS when combined with ET for the treatment of CGH.

Methods: Adults (aged 18–65), blinded to treatment arm, will be randomized into one of two groups: active tDCS followed by ET or sham tDCS followed by ET. Transcranial direct current stimulation will be applied over M1 three times per week for 6-weeks and ET will be performed daily. The primary outcomes of this trial will be the feasibility and safety of the intervention. Feasibility will be defined as greater than 30 % recruitment, 70 % protocol adherence, and 80 % retention rate. Safety will be defined as no severe adverse events. Secondary exploratory outcomes will assess improvement in pain, strength, function, and quality of life.

Conclusions: This trial aims to demonstrate the safety and feasibility of tDCS in combination with ET for the treatment of CGH. Cervicogenic headaches can be difficult to treat contributing to significant impairments function and quality of life. Transcranial direct current stimulation is a potential novel treatment to improve health outcomes in these patients.

Registration: ClinicalTrials.gov-NCT05582616.

1. Background

Annually, approximately 450,000 Canadians will experience a mild traumatic brain injury (mTBI) [1] and approximately 125,000 Canadians will experience a whiplash injury [2]. However, both numbers are underestimates as many individuals do not seek acute medical care for these injuries [3]. In individuals with whiplash, up to 27 % will experience cervicogenic headaches (CGH) acutely [4]. Furthermore, in those with mTBI, up to 58 % will experience post-traumatic headaches one year post-injury which includes CGH [5]. Symptoms of CGH include restricted mobility, local tenderness of the upper cervical spine joints, weakened cervical flexor and extensor muscles, local sensitivity to pressure and bilateral desensitization to temperature [6–8]. These symptoms can result in significant functional impairment including reduced social, occupational, and recreational abilities due to considerable symptom burden. For instance, up to 35 % of those with post-traumatic headaches, including CGH, are unable to work 3 months after onset [9]. Furthermore, CGH were responsible for approximately

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500 million dollars per year in treatment costs alone in 2017, with that figure likely to have grown in more recent years [10]. Presently there is no curative treatment option for CGH and as such, current treatments such as pharmacotherapy and manual therapy rely on a trial-and-error approach, often leading to only partial improvements. There is a need for novel interventions to help improve pain, functional impairments and detriments to quality of life that are associated with CGH.

Cervicogenic headaches (CGH) are a pain disorder, whereby pain is perceived in the head, but primarily attributed to dysfunction of the cervical spine and supporting muscle and connective tissues [11]. More specifically, the pathogenesis of CGH is the result of pain from the cervical spine being perceived in the face and head due to the convergence of nociceptive afferents from the upper three cervical nerves and trigeminal nerves onto second-order neurons in the trigeminocervical nucleus [11]. As a result of this convergence nociceptive afferents in the face and head are excited resulting in perceived pain in these areas [6]. Peripherally, CGH can occur from injury to the first three cervical spinal nerves (C1, C2 and C3) and their rami, with descending central pathways modulating pain perception [12]. Often through trial and error, pharmacotherapy including analgesics and C2-C4 facet joint injections can provide temporary relief of pain and improve function resulting in only modest symptom improvements [13–15]. Furthermore, radiofrequency ablation is often attempted as a longer-term solution but only provides approximately 30–50 % relief with respect to pain intensity in those that are eligible to receive it [16].

Another common intervention type are conservative therapies, including any interventions which do not involve medications or invasive procedures, such as manual therapy (MT) and exercise therapy (ET). These interventions focus on addressing associated physical mobility, strength or endurance impairments of the neck and scapulothoracic regions through spinal mobilization and manipulation of muscles surrounding the cervical spine in the case of MT and through isometric holds, craniocervical flexion, and meeting resistance in the case of ET [17–21]. In an early seminal trial for CGH, participants performing regular craniocervical flexion to improve the motor control of deep neck flexors had significantly reduced headache frequency and intensity, with associated reduction in neck pain [17]. However, a recent systematic review focused on MT and ET for CGH demonstrated much more modest benefits with small effect sizes and short term benefits [21]. More specifically, eight trials focused on MT were assessed and while most had a low risk of bias and significant benefits when compared to sham or alternative treatments, only three trials demonstrated a clinically important difference at short or long-term follow-up [21]. Furthermore, two trials focused on ET but both had high risk of bias and only one of two demonstrated clinically important improvements in headache burden [21]. As such, this review demonstrates the conflicting nature of current evidence for the use of MT and ET in treating CGH.

One novel approach for treating CGH involves using non-pharmacologic interventions, such as neuromodulation therapy, to normalize neuronal signaling and excitability by applying external electrical current or magnetic fields. Transcranial direct current stimulation (tDCS) is one such method of neuromodulation during which an electrical current is applied to specific regions of the brain in order to influence activity in an attempt to limit pathogenic neuronal signalling [22,23]. During anodal tDCS, a negative anodal electrode is placed over the target stimulation site and a positive cathodal electrode is placed over a neutral site, generally the supraorbital or occipital regions. Electrical current is applied traveling from the anode into the brain and then through the cortex around the stimulation site to the cathode, while this electrical current does not cause action potentials itself, it alters the resting potential of neurons to change firing patterns [24].

Numerous studies using tDCS as an intervention for brain injury [23], stroke [25], neurodegenerative disease [26], depression [27], and anxiety [28] have shown improvements in cognition, motor control, and mood. While no previous tDCS studies have explored treatment of CGH, there are studies involving patients with migraines, which is also a common post-traumatic headache phenotype and has common symptoms including neuralgia, facial pain, and dysfunction of musculature supporting the cervical spine [29–33]. Notably, Aksu et al. and Andrade et al. demonstrated significant reduction in headache frequency, headache intensity, and improvements in quality of life in active tDCS compared with sham tDCS for patients with migraine headaches following anodal tDCS stimulation over the primary motor cortex (M1) [30,31]. Furthermore, several tDCS studies have explored tDCS over the M1 as a treatment for chronic pain conditions including osteoarthritis and neuropathic pain [34–37]. Recently, Yeh et al. and Bonifácio de Assis et al. both noted significant reductions in pain intensity following active anodal M1 tDCS when compared to sham tDCS for participants with chronic neuropathic pain [34,35]. Despite promising results for the use of tDCS in treating chronic pain and primary headaches, there are no previous sham-controlled trials evaluating the use of tDCS in patients with CGH.

To optimize benefits from tDCS therapy, combination with ET has been shown to improve further reduce pain intensity and improve functional outcomes such as strength and mobility.[38]Given that patients with CGH often experience poor neck mobility and strength impairing function and that ET has already been considered in prior studies to correct this [17,18], there may be benefit in combining tDCS with ET in patients with CGH. This is supported by previous studies, where it was shown that anodal M1 tDCS combined with ET focused on knee strength improved motor learning and pain processing in individuals with knee osteoarthritis [36,37]. This was demonstrated by a reductions in the perception of pain intensity at follow-up and improved knee strength compared to groups receiving sham tDCS with ET. As such, studies evaluating the combination of tDCS and ET to improve pain and function have been promising in osteoarthritis and tDCS alone has shown promise in migraines and chronic pain conditions, however, no study has examined the complimentary effects of tDCS and ET in patients with CGH.

The specific objectives of this study are as follows.

1. The primary objective is to evaluate the safety and feasibility of tDCS and ET as a treatment for patients with CGH. Feasibility goals were set based on previous feasibility trials [39–41] and included a recruitment rate of 30 % for those contacted about the study, intervention completion rate of 70 % within 6-weeks with respect to both tDCS and ET, and a retention rate of 80 % to the completion of treatment. With respect to safety, adverse events will be tracked and separated based on criteria from the national health institute whereby adverse events not requiring medical attention are considered minor and those requiring medical attention were considered major [42]. The objective of this study with respect to safety is to have no major adverse events including but not limited to fainting spells, seizures, and severe mental health concerns based on recommendations from previous tDCS safety studies and safety studies in other headache disorders [40,41,43,44]. Adverse events and within session changes in symptom burden will be tracked using a previously established tDCS safety questionnaire [41] and minor adverse events as well as within session changes in symptom burden will still be reported.
2. The secondary exploratory objectives are to evaluate headache pain intensity, headache frequency, pain sensitivity, neck strength and endurance, quality of life, anxiety, and depression - as measured by questionnaires and physical assessments which are described in the methods - following active tDCS treatment combined with ET compared to ET alone in patients with CGH.

2. Methods

2.1. Study design

This study will be a randomized, sham-controlled, double blind

(participant and assessor), pilot trial evaluating the safety and feasibility of tDCS in conjunction with ET as well as benefits with respect to symptom burden in adults diagnosed with CGH using the International Classification of Headache Disorders – 3 (ICHD-3) criteria [45]. Diagnosis will be made by a physiatrist, neurologist, or specialist physiotherapist with experience treating CGH. Participants will be screened for eligibility and then randomized 1:1 into active and sham tDCS, they will then complete 6 weeks of tDCS with ET, following this they will be followed up with at post-treatment, 6-weeks, and 12-weeks post-treatment. This is further visualized in Fig. 1.

2.2. Study registration

This study was registered on October 4, 2022, on ClinicalTrials.gov (NCT05582616) and was approved by the University of Calgary ethics review board on November 3rd, 2022 (REB22-0890). The study completed enrolment by the time of publication but was still enrolling at the time of submission. The study protocol was reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trial reporting which ensure that necessary components for stringent study design are present [46].

2.3. Study setting and recruitment

Recruitment will occur through community and specialist health care clinics in Calgary, Alberta, Canada and surrounding communities. Posters will be distributed to any centre with one of the healthcare professionals needed to make a diagnosis (physiatrist, neurologist, or specialist physiotherapist). Any patients at these centers will be able to complete a digital 'consent to contact' survey through a QR code on the study poster. Once signed, participants will be contacted immediately with information regarding the study and provided with a full consent form (Appendix I). If they choose to consent, participants will be screened for inclusion/exclusion criteria via telephone and subsequently enrolled in the study if deemed to be eligible. After successful screening, treatment group will be allocated by a researcher uninvolved in the study. All assessment and treatment procedures will occur at a local community multidisciplinary chronic musculoskeletal pain centre (Vivo Cura Health, Calgary, Alberta, Canada).

2.4. Study participants

Inclusion – Thirty-two participants will be recruited who fulfill the ICHD-3 criteria for CGH as established by a physiatrist, neurologist, or specialist physiotherapist with experience treating CGH (Table 1) [45]. The proposed sample size is based on previous recommendations indicating a total sample of between 24 and 50 participants is best practice for feasibility studies [47,48]. Additionally, sample sizes of 10–20 per group have been recommended for pilot studies considering group-time interactions [49]. Eligible participants can be from any sex/gender but must be between the ages of 18–65 (targeting an adult population) and have chronic (3 or more headaches per week for >12 weeks) CGH meeting IHCD-3 criteria. In addition, participants must have an average numeric pain rating scale score of ≥4/10 in the past week and a neck disability index score of >14/50 at the time of screening. Participants will not be excluded for the use of concurrent therapies but will be asked to report these therapies and any changes in their usage throughout the trial. Reporting of changes in therapies will occur through a medication usage questionnaire administered at each follow-up. *Exclusion* – Participants will be excluded for having known spinal pathology (tumour, fracture, etc), nerve root pain/sensory loss or systemic muscular, joint (e.g. inflammatory), or neurological conditions based on self-reporting and confirmation with referring care provider. Furthermore, they will be excluded if they have undergone recent head or neck surgery (within prior year) or have contraindications to tDCS as established by self-report. Contraindications to tDCS include exposed skin near electrode sites or other skin conditions such as dermatitis, metal or electronic implants, prior surgery on head or spinal cord, history of epilepsy or seizures, history of fainting spells or syncope, pregnancy or chance of pregnancy, and previous electrical stimulation.

2.5. Blinding and randomization

Following screening and enrolment into the study, participants will be randomized into one of two groups: active tDCS with ET or sham tDCS with ET. Randomization will occur via a sealed envelope where participant identifier numbers have been randomly assigned active or sham tDCS by a research assistant who is uninvolved with the study using a random number generator and kept away from other researchers throughout the study to maintain concealment. Following screening and enrolment, the external research assistant will notify the researcher performing the screening and administering tDCS of participant allocation to ensure allocation is unbiased by the screening process. All participants will undergo an initial assessment and a further 18 sessions of tDCS and ET (Fig. 1). Participants in the sham group will be blinded using a previously established blinding method [50]. They will undergo a 30 s ramp up period, during which, the current will be gradually increased and then the machine will turn off. The 30 s ramp up period was to provide an initial sensation of stimulation. At the post-treatment follow up participants will be asked to indicate the treatment group they believed they were a part of to assess the efficacy of the blinding method through a comparison of the percentage of participants choosing correctly in each treatment group. Assessors and care providers will be blinded to the participants grouping. The researcher administering the tDCS will not be blinded during treatment, however, this researcher will not be responsible for administering any assessments and data will be re-coded during analysis to blind this researcher during analysis.

2.6. Interventions

Transcranial Direct Current Stimulation – Transcranial direct current stimulation will be administered for 18 sessions over 6 weeks (3 per week). This session number and frequency were chosen based on previous systematic review of tDCS in chronic headaches as well as ET recommendations for CGH of 6-weeks for a minimum program duration [17,51]. A safety questionnaire will be administered before and after each tDCS session (sham or active) to measure transient adverse effects. This questionnaire assessed symptoms of itching, tingling, burning, headache, fatigue, nausea/dizziness, and feelings of anxiety or depression as well as any adverse events between sessions. Transcranial direct current stimulation will be administered to the M1 anodally with the cathode placed over the supraorbital region. M1 will be found through measurements of the head. First, the point halfway between the nasion and inion as well as halfway between the left and right tragus will be found. Then the anode will be placed 20 % of the inter-tragi distance below this point towards the side of worse pain as has been previously described as an accurate method for finding M1 [52]. M1 was chosen as the treatment target based on positive prior results with systematic reviews of tDCS for the treatment of both chronic pain conditions and migraines demonstrating a large number of studies using M1 anodal stimulation with a high degree of success [51,53]. Furthermore, previous literature has proposed that M1 stimulation leads to pain reduction through engagement of the descending pain modulatory network, through reduced connectivity between the thalamus and prefrontal pain centers, and through residual stimulation of the somatosensory cortex which is also involved in pain sensation [54–57]. However, the exact mechanism is largely unknown. Finally, stimulating M1 in combination with ET may result in improved motor learning and response to ET which will indirectly lead to pain reduction [37,58]. Transcranial direct current stimulation will be delivered via two 35 cm^2 sponges at 2 mA in the active group and 0 mA in the sham group, tDCS will be administered for 20 min with a 30 s fade in and 30 fade out period. These parameters

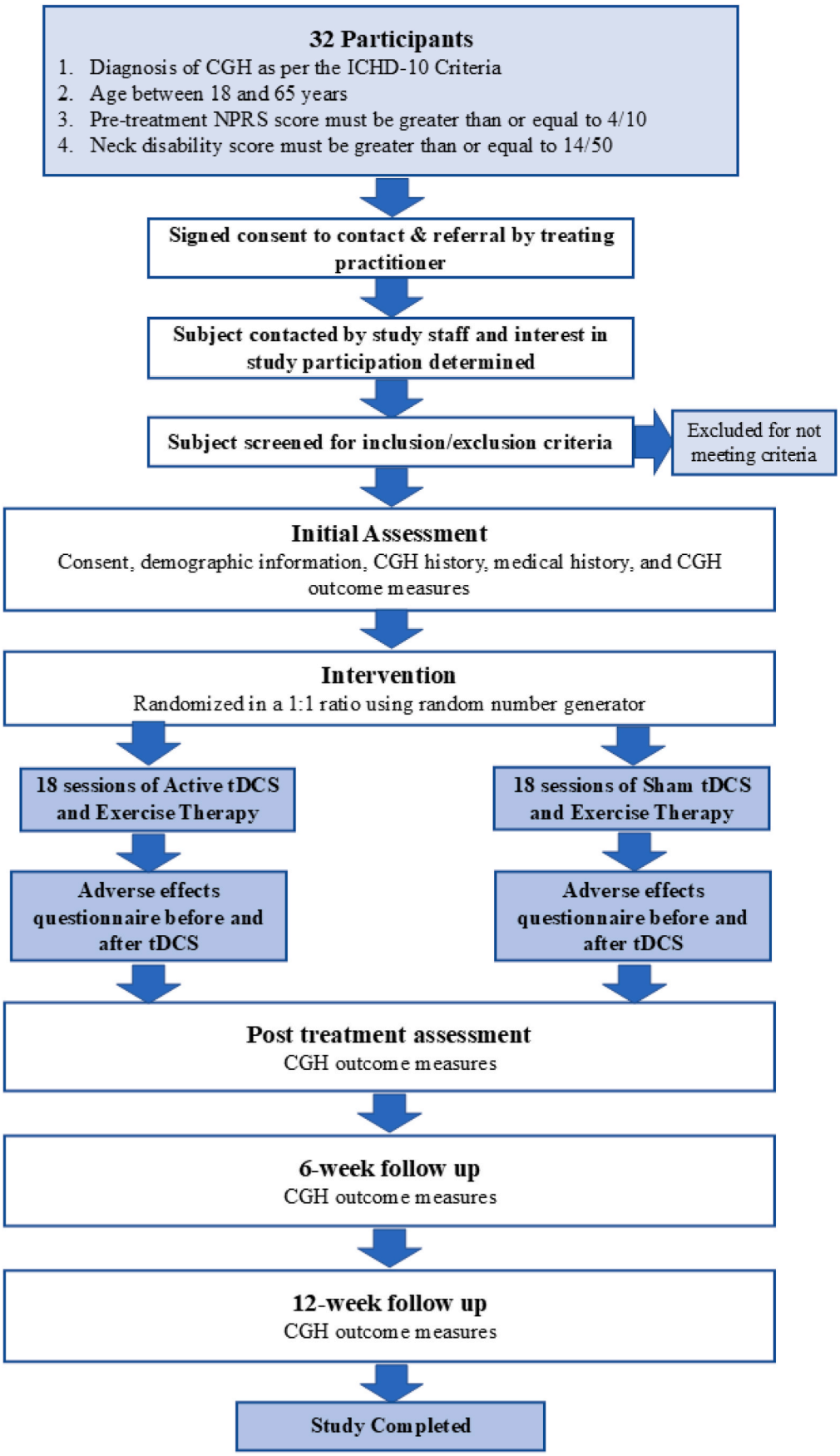

Fig. 1. Flowchart of study design; CGH outcome measures include: 2-week headache diary, HIT-6, HDI, EQ-5D, RPQ, medication usage questionnaire, PHQ-9, GAD-7, NPRS, PROMIS pain interference scale, PCS, CCFT, CEET, CFET, DNSA, RCMT, and MECJ.

Table 1
International Classification of Headache Disorders 3rd Edition (ICHD-3) diagnostic criteria for cervicogenic headaches [27].

A	Any headache fulfilling criterion C
B	Clinical and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache
C	Evidence of causation demonstrated by at least two of the following: 1. Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion 2. Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion 3. Cervical range of motion is reduced, and headache is made significantly worse by provocative maneuvers 4. Headache is abolished following diagnostic blockade of a cervical structure or its nerve supply
D	Not better accounted for by another ICHD-3 diagnosis

are consistent with many tDCS studies for headache and chronic pain disorders from the previously discussed systematic reviews [51,53]. *Exercise Therapy* - ET will be provided based on a recommended upper quadrant rehabilitation program, directed at participants' physical impairments, from a specialist physiotherapist with experience in treating CGH based on a previous program that was shown to be effective by Jull and colleagues [17]. The program focuses on building endurance and strength in scapulothoracic muscles required for the maintenance of posture, flexor and extensor muscles of the neck, and improving motor control of the deep cervical flexor muscles [17,59]. This program is performed at a level that is pain free and progressed to more challenging levels as participants improve at the discretion of the study physiotherapist (Author AS) based on recommendations included in the original study by Jull and colleagues. Participants were asked to perform ET in the clinic following tDCS sessions on days when tDCS was to be administered. Performing ET following tDCS has been shown to be more beneficial than ET prior to tDCS in a recent systematic review which demonstrated larger effect sizes with this ordering, additionally, it has been shown that the physiological effects of tDCS occur approximately 5 min to 1 h after stimulation [38,60]. Exercise therapy sessions performed at the clinic were done at the guidance of physiotherapists or research staff to allow for form correction. Participants were also asked to perform the ET program on days when they were not attending the clinic and were provided videos of the exercises assigned to help with form. Adherence to the ET program on these days was self-reported by participants to assess feasibility of this intervention.

2.7. Measures

Following enrollment participants will be administered questionnaires to collect demographic data including age (years), sex (male/female/intersex), litigation status (yes/no), employment status (full-time/part-time/unemployed), education level (less than grade 12/grade 12/trades or vocational studies/bachelor's degree/master's degree/doctorate), handedness (right/left/ambidextrous), activity level (minutes of strenuous activity/minutes of moderate activity/minutes of mild activity), and medical history unrelated to CGH (other medical conditions). Furthermore, these initial questionnaires will collect details surrounding headache history including time since onset (months), mechanism of onset (motor vehicle collision/sports and recreation/fall/arthritis or degenerative disc disease/other), comorbid headache phenotypes (migraine or tension-type), number of concussions (0/1/2/3/4/5 or greater) and whiplash injuries (0/1/2/3/4/5 or greater), and current treatments (physiotherapy, nerve blocks, medications). Due to the size and nature of this trial, most of these metrics will not be included in the analysis, however, age and sex will be accounted for in the analysis and other measures contribute to describing the population. Prior to treatment participants will also complete questionnaires regarding symptom burden that are described below and will complete a physiotherapy assessment performed by a licenced physiotherapist with experience treating CGH (Author AS). These will be re-done post-treatment and at 6- and 12-weeks post-treatment (Fig. 1). Follow-up length was chosen based on previous tDCS trials in chronic pain and headache populations [51,53].

2.8. Primary outcomes

The primary outcomes of this trial will focus on assessing the safety and feasibility of active tDCS combined with ET for the treatment of CGH. This pilot trial is smaller in nature and aims to inform a larger clinical trials regarding the safety and feasibility of this combination intervention and sample sizes. Specific outcomes to evaluate feasibility and safety were determined in part by a previous feasibility studies [39–41] and safety studies [40,41,43,44] using tDCS in other populations. More specifically, the exact goals referenced were achieved in many of these pilot trials and are indicative of a feasible and safe intervention.

1. Recruitment: Able to recruit at least 30 % of the individuals who are screened for participation.
2. Intervention attendance: at least 70 % of sessions (tDCS and daily exercise) are completed within 6 weeks by each individual participating in the trial.
3. Retention: at least 80 % of participants starting the trial remained in the trial until the end of treatment.
4. Adverse effects/events: There will be no serious adverse events (defined as those requiring medical intervention) [42]. All other adverse events and transient effects of tDCS will be described and compared between the active and sham tDCS groups.

2.9. Secondary outcomes

Secondary outcomes will be assessed to explore the effects of this intervention on various aspects of symptom burden relating to CGH. The **headache impact test-6 (HIT-6)** will be used to assess headache intensity through 6-items focused on the impact of headaches on daily life. Each item receives a score of 6 for "never", 8 for "rarely", 10 for "sometimes", 11 for "very often", and 13 for "always". This results in a minimal score of 36 indicating no impact on daily life from headaches and a maximal score of 78 indicating a severe impact on daily life because of headaches. The HIT-6 has a high internal consistency in patients with chronic migraine (Cronbach $\alpha = 0.87$) [61]. Furthermore it has been shown to have an MCID of 8 points in a chronic headache patient population [62]. **Headache diaries** will be used to determine the frequency and duration of headaches through a questionnaire completed each day for a two-week period. Headache diaries will be administered two weeks prior to tDCS treatment, for two weeks after completion of tDCS treatment and two weeks prior to the 6- and 12-week post treatment follow-ups. Participants will be first asked if they experienced a headache that day, if so the number of hours, average headache pain (on an 11-point scale from 0 to 10), location of the pain, and information about medication usage will be recorded. Headache diaries have been validated in patient populations with chronic headaches through comparisons with other headache questionnaires and have shown a high test-retest reliability ($r = 0.68–0.79$) [63]. The **headache disability index (HDI)** was used to determine the functional impacts of headaches on various daily activities. It is a 25-item measure which asks participants to evaluate whether they experienced certain functional impairments with a score of 0 for "never" a score of 2 for "sometimes" and a score of 4 for "always". This measure had a minimal score of 0 for no functional impairments and a maximal score of 50 for extreme functional impairments. The questionnaire has a high internal consistency (Cronbach $\alpha = 0.91$) in patients with chronic headaches [64]. The **numeric pain rating scale (NPRS)** will be used for quantifying intensity of pain. It is a scale graded from 0 to 10 (11 points) with 0 defined as "no pain" and 10 as "worst possible pain". Individuals will be asked to

rate their current level of pain as well as their highest and lowest level of pain over 24 h and the 3 scores of pain intensity were averaged to give a total score. The NPRS has been validated for measuring pain intensity with a high test-retest coefficient (r = 0.95) in individuals with chronic neck pain [65]. Furthermore, in individuals with chronic pain from spinal cord injury the NPRS has been shown to have an MCID of 1 point or a 15 % change in score [66]. The **pain catastrophizing scale (PCS)** will be used to quantify impaired perception of pain by individuals. It consists of 13 items focused on how much individuals think about pain. Each question will be scored on a scale from 0 to 4 (5 points) with 0 defined as "not at all" and 4 as "all the time". The PCS has a high internal consistency (Cronbach α = 0.91) and an MCID of 4.5 in a chronic pain population [67,68]. Additionally, in chronic pain populations a higher PCS score is associated with increased disability in a clinically significant manner [69]. The **patient reported outcomes measurement information system – pain interference scale (PROMIS-PI)** will be used for quantifying interference of pain with daily activities. It consists of 4 items focused on how much pain interferes with different aspects of an individual's daily life. Each question will be graded from 1 to 5 (5 points) with 1 defined as "not at all" and 5 defined as "very much". The PROMIS pain interference scale has a high internal consistency (Cronbach α = 0.94) in patients with fibromyalgia [70]. Furthermore, it has an established MCID of 5.5 points in a chronic pain patient population [71]. The **rivermead post-concussion symptom questionnaire (RPQ)** will be used to assess common symptoms after concussion. The RPQ is a 16-item scale where participants rated the occurrence of common concussion symptoms on a 5-point scale (0–4) from "not experienced" to "severe problem". It has demonstrated high internal validity with a high test-retest coefficient (r = 0.89) in patients with persistent post concussive symptoms and an MCID of 4.6 points [72,73]. The **European quality of life 5-dimension** (EQ-5D) will be used for quantifying quality of life. It consisted of 5 items or categories focused on mobility, self-care, ability to do usual activities, pain, and anxiety/depression. Each of these will be graded from 1 to 5 (5 points) with 1 defined as "no problems" and 5 defined as "unable to perform" or "extreme". Finally, the EQ-5D includes a visual analog scale where individuals rate their health from 0 to 100 where 0 is "poor" and 100 is "excellent". In a chronic pain population, the EQ-5D has a moderate internal consistency (Cronbach α = 0.74) [74]. Furthermore, in a chronic pain patient population the MCID for the EQ-5D is any improvement (1-point) [75]. The **generalized anxiety disorder-7 (GAD-7)** will be used to assess symptoms of anxiety, it consists of 7 symptoms and the frequency individuals experience these symptoms over the past 2 weeks will be scored. Each of these will be scored from 0 to 3 with 0 defined as "not experienced at all" and 3 defined as "experienced every day". The GAD-7 has been validated in the general population with a high internal consistency (Cronbach α = 0.89) [76]. The **patient health questionnaire-9 (PHQ-9)** will be used to measure symptoms of depression, it consists of 9 symptoms and the frequency individuals experienced these symptoms over the past 2 weeks will be scored. Each of these will be scored from 0 to 3 with 0 defined as "not experienced at all" and 3 defined as "experienced every day". The PHQ-9 has a high sensitivity (88 %) and specificity (88 %) in the general population demonstrating high reliability as a measure of depression [77]. Furthermore, during each physiotherapy assessment the following measures were collected by a licenced physiotherapist. The **cervical flexor endurance test (CFET)** and **cervical extensor endurance test (CEET)** will be used to measure the extensor and flexor endurance in the cervical spine. These tests will be performed by recording the time an individual can lift their head just off a bed while lying on their front (extensors) and back (flexors). These tests have been validated with high inter-rater reliability coefficients (k = 0.68–0.8) in patients experiencing chronic neck pain [78,79]. Furthermore, an MCID of 19.15 s has been established in patients with chronic neck pain for the CFET while an MCID of 73.00 s has been established for the CEET in patients with chronic neck pain [80,81]. The **cervical isometric strength test (CIST)** will be used to measure the strength of cervical muscles in the neck in each direction. A MicroFet 2 handheld dynamometer (Hoggan Scientific, Salt Lake City, UT, USA) will be placed on the participants head on the front, back, and each side and then force will be gradually applied [82]. The participants will be asked to meet this force and the test was stopped when they were no longer able to resist the force being applied. The CIST has demonstrated reliability with a high test-retest coefficient (r = 0.94–0.97) in healthy controls and an MCID of 139.25 N when all four directions are added in patients with chronic neck pain [82]. The **craniocervical flexion test (CCFT)** will be used to measure fine motor control of the deep cervical flexor (longus colli and capitus) muscles. Participants lay supine and will be asked to nod their head to activate the deep muscles, without activating the superficial cervical flexors (sternocleidomastoid and scalenes). Scoring will be based on the maximum pressure (mm-HG) that participants can successfully exert for 10 s on a pressure biofeedback cuff (Chattanooga Group Inc., Hixson, TN, USA) placed under their neck whilst performing the nodding motion, without activation of the superficial cervical flexors. This test has been validated in healthy controls with an intra-rater reliability of 0.98 [83]. In addition, in patients with chronic neck pain the MCID has been shown to be 2.00 mm-HG [80]. The **range of motion test (ROM)** will be used to measure the range of motion for movements involving the cervical spine. Participants will start sitting upright with neutral posture unsupported and will be asked to move their head in six different directions – flexion, extension, side flexion to the right and left, and rotation to the right and left. Only one repetition will be measured in each direction using a cervical range of movement device CROM (Performance Attainment Associates, St. Paul, MN, USA) [84]. This test has been validated in healthy controls with a high test-retest coefficient (r = 0.89–0.98) and an MCID of 33° when all directions are added [80]. The **manual examination of upper cervical joints (MECJ)** will be used to measure the physical impairment of each cervical joint independently. A licenced physiotherapist will manually apply pressure on upper cervical facet joints known to be associated with cervicogenic headache (i.e. C1/2–3/4) and ask participants to rate pain in each joint (on an 11-point scale from 0 to 10) [85]. This test been validated in patients with neck pain and has a high inter-rater reliability (κ = 0.53–0.76) [86].

2.10. Recruitment

Clinicians at recruitment sites will be informed of the benefits of the intervention through a letter describing the study and will be asked to discuss involvement with patients who meet criteria with study information and a consent to contact form. Members of the research team will also be contacting physicians and physiotherapists at each centre every 3–6 months to remind them of participant criteria and that the study is still ongoing.

2.11. Attrition and adherence

All participant data will be included in the final analysis to explore the feasibility of the trial. In particular we expect to retain all feasibility and safety data, and any missing questionnaires will not pose an issue due to the use of linear mixed effect models to evaluate secondary outcomes. Participants will be encouraged to complete the 18 tDCS sessions within 6 weeks and exercise daily, with weekly reminders and easy access to study team. However, they will be offered the chance to make up any missed sessions after the initial 6 weeks and the number of weeks required to complete 18 sessions will be recorded. This will not be accounted for in the analysis but will be reported for reproducibility in future trials utilizing this intervention and patient population. Participants will be given daily reminders via text (Twilio, 2022) at times when the headache dairies are being administered to try to encourage completion of the diaries, texts will contain a link to the diary for that day. If a participant experiences further injury which aggravates CGH symptoms or changes their current treatments/medications, data for any

subsequent timepoints will be removed, existing data points will be kept to avoid bias. This removal is deemed necessary as re-injury or changes in treatment plan can dramatically affect the rating and presence of symptoms associated with CGH.

2.12. Data management and monitoring

Participants will be assigned a study ID upon enrolment and all collected data will be stored in a REDCap database protected by two factor authentication and updated encryption (REDCap 12.4.0, 2022 from Vanderbilt University). Only the research team will have access to this data. No paper documents will be maintained, if any are created, the information will be transferred to REDCap and then the documents will be shredded and de-identified data will be retained digitally for 5 years following Health Canada policy C.08.004.1 guidelines. An official data monitoring committee will not be required due to the low safety risks associated with this trial; the absence of a data monitoring committee was approved by the University of Calgary Conjoint Health Research Ethics Board. However, the principal investigator and co-investigators will meet in the case of any adverse events to discuss potential contributing factors and disclosure to the University of Calgary Conjoint Health Research Ethics Board will be made to determine whether the trial should proceed. Participants will be asked to report adverse effects at the beginning of each treatment session and any effects will be managed with support of the study physician (Author CTD) and any other care providers involved in each participants regular care. If unblinding is required for safety concerns this will be done at the discretion of the study physician and University of Calgary Conjoint Health Research Ethics Board and will only be done in the case that this information is required for treatment of the participant. Study team members and care providers will be unblinded by the research assistant keeping the allocation envelopes.

2.13. Data analysis

Recruitment and retention rate, along with adherence and safety data will be reported through descriptive statistics. Data will be reported as percentages and counts for categorical data and mean and standard deviation for continuous data. It is not expected that there will be missing data for these outcomes but if this occurs then participants will need to be removed from the analysis and this will be disclosed. For exploratory outcomes, scores on each assessment will be compared from pre-to post-treatment as well as 6- and 12- week follow ups. Follow-up time points were chosen to evaluate clinical changes for up to 12 weeks following treatment. Furthermore, comparison will be made between the sham and active tDCS groups. Linear mixed effect models for the primary and secondary outcome variables will be used to consider differences between timepoints and treatment groups, this will reduce any influence of multiplicity by accounting for the longitudinal nature of the data. Demographic variables will also be factored into the linear mixed effect model to adjust for age and sex through the addition of these terms in the model. These variables were chosen a priori as we expect them to have the most considerable influence on the outcomes, however, if we find through the analysis that other variables have a more considerable effect these will be accounted for instead. Due to the limited sample size, it would not be statistically feasible to additionally account for more than two confounding variables and as such key variables such as sex can not be accounted for. While this is certainly a limitation of the study, any publications will include recommendations to account for sex in future studies with larger sample sizes. All results will be presented with 95 % confidence intervals as well as p-values to convey the precision of estimates.

2.14. Study status

At the time of submission, participants were being recruited and enrolled in the study (consent form in Appendix I).

2.15. Protocol amendments

Modifications to the protocol will be submitted and approved through the University of Calgary Conjoint Health Research Ethics Board. The ClinicalTrials.gov registry will be updated as required, and trial participants will be notified of pertinent study modifications.

2.16. Access to data

The principal investigator, co-investigators, research assistants, students and statistician colleagues who are directly involved in the study will have access to the data collected. However, the assessors and external research assistant who will be recoding the data prior to analysis will not have access to the data until study completion.

2.17. Dissemination policy

Study results will be disseminated through presentations at conferences, invited presentations, and published manuscripts by study authors and other contributors. The study is registered on clinicaltrials.gov. There will be no use of professional writers.

3. Discussion

CGH impacts many people each year, especially following concussion and whiplash injuries [8]· [9]· [11]. The condition is associated with chronic pain, headaches, and mobility issues with limited effective treatment options. One potential long-term treatment option for CGH is ET. However, recent exercise trials have demonstrated conflicting results [17–21]. M1 tDCS has been identified as a promising treatment option for other chronic pain conditions such as migraines and arthritis [32,33,36,37]. Furthermore, M1 tDCS has demonstrated the potential to improve motor learning ability [25]. Therefore, this trial proposes combining M1 tDCS with ET to determine the safety, feasibility, and efficacy of this intervention. Participants may experience a reduction in headache intensity, duration, and frequency, as well as reduced pain intensity and sensitivity and improved neck function in turn improving overall quality of life and activities of daily living. The outcomes from this pilot study aims to provide information to support a phase 2 clinical trial. Feasibility and safety will be assessed through recruitment and retention rates as well as adherence to the study protocol and adverse effects data. A preliminary exploration of efficacy to evaluate M1 tDCS to reduce CGH symptom burden will be conducted through measures of pain intensity and sensitivity, headache intensity, duration, and severity, and neck function.

4. Ethics approval and consent to participate

This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB#22–0890) and all prospective participants will be informed regarding the study risks and then provided with a consent form outlining the risks of the study. Only once the consent form has been signed will screening, treatment, and follow-up activities occur.

5. Consent for publication

Not Applicable.

Availability of data and materials

Data is not available as only participant data will be collected and this is protected via ethics, materials have been made available in manuscript.

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Authorship eligibility guidelines

Contributions to study conception or design AND/OR major contributions to writing of the manuscript.

CRediT authorship contribution statement

K. Jobin: Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **C. Campbell:** Writing – review & editing, Visualization, Methodology, Formal analysis. **S.M. Schabrun:** Writing – review & editing, Methodology, Conceptualization. **K.J. Schneider:** Writing – review & editing, Supervision, Methodology, Formal analysis. **A. Smith:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **C.T. Debert:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Not Applicable.

Abbreviations:

mTBI – Mild Traumatic Brain Injury
CGH – Cervicogenic Headache
ET – Exercise Therapy
tDCS – Transcranial Direct Current Stimulation
M1 – Primary Motor Cortex
ICHD-3 – International Classification of Headache Disorders 3
NPRS – Numeric Pain Rating Scale
HIT-6 – Headache Impact Test 6
RPQ – Rivermead Post-concussion Symptoms Questionnaire
HDI – Headache Disability Index
EQ-5D – European Quality of Life Five Dimension
QAQ-A – Section A of the Quantitative Analgesics Questionnaire
PHQ-9 – Patient Health Questionnaire-9
GADS-7 – Generalized Anxiety Disorder Scale-7
PROMIS – Patient Reported Outcomes Measurement Information System
PCS – Pain Catastrophizing Scale
CCFT – Cranio-cervical Flexion Test
CEET – Cervical Extensor Endurance Test
CFET – Cervical Flexor Endurance Test
DNSA – Dynamometry Neck-strength Assessment
RCMT - Range of Cervical Movement Test
MECJ - Manual Examination of the upper Cervical Joints

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101370.

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