Comparative Effectiveness of Intermittent Neuromuscular Electrical Stimulation Versus High-Fruit-and-Vegetable Dietary Intervention as Complementary Therapies in Cervicogenic Headache Management: A Randomized Controlled Trial with Mechanistic Outcomes

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Abstract

Cervicogenic Headache (CGH), originating from cervical musculoskeletal dysfunction and associated neuropathological cascades, represents a significant clinical burden affecting 2.5-4.1% of the global population with limited evidence-based complementary intervention strategies. This randomized controlled trial evaluated the comparative effectiveness of Intermittent Neuromuscular Electrical Stimulation (INES) versus High Fruit-and-Vegetable (HFV) dietary intervention as adjuncts to standard physiotherapy in 84 adults with chronic cervicogenic headache (mean duration 18.4±5.2 months).

Participants were stratified and allocated to three parallel groups: standard care alone (SC, n=28), SC combined with INES (n=28), or SC combined with HFV dietary protocol (n=28) for 12 weeks with 4-week follow-up assessment. Primary outcome measures encompassed headache intensity (Numerical Pain Rating Scale, NRS 0-10), headache frequency (days per month), and cervical range of motion. Secondary measures included Neck Disability Index (NDI), Pressure Pain Threshold (PPT) at cervical landmarks, upper cervical mobility (flexion-rotation test), serum inflammatory biomarkers (interleukin-6, C-reactive protein, tumor necrosis factor-alpha), and cervical proprioception assessed via active head repositioning test. Quantitative outcome assessment occurred at baseline, 6 weeks, 12 weeks, and 4-week follow-up. Both interventions significantly outperformed standard care ($p<0.001$). INES demonstrated superior efficacy for acute pain reduction, with mean NRS improvement of 4.2±1.1 points compared to HFV reduction of 2.9±1.0 points ($p=0.002$) and headache frequency decrease of 12.3±3.2 days/month versus 9.1±2.8 days for HFV ($p=0.003$). Conversely, HFV intervention yielded enhanced anti-inflammatory benefits, reducing serum CRP by 2.1±0.7 mg/L and IL-6 by 1.9±0.6 pg/mL ($p <0.05$), with sustained pressure pain threshold improvements of 1.8±0.5 kPa. INES facilitated faster neuromuscular modulation with trajectory superiority evident by week 6, whereas HFV demonstrated progressive systemic anti-inflammatory effects with delayed but durable outcomes. Graph analysis revealed distinct intervention trajectories: INES showed acute neuromuscular benefits with plateau at week 8, while HFV exhibited linear progressive improvement throughout the 12-week intervention period. Combined analysis suggests complementary mechanistic pathways - INES addressing neuromuscular dysfunction and proprioceptive deficiency, while HFV targets systemic neurogenic inflammation and central sensitization mechanisms. These findings support investigation of combined approaches for comprehensive cervicogenic headache management addressing both immediate neuromuscular dysfunction and underlying inflammatory pathophysiology [1-4].

Keywords: Cervicogenic Headache; Neuromuscular Electrical Stimulation; Dietary Intervention; Polyphenol-Rich Diet; Inflammatory Biomarkers; Cervical Proprioception; Mechanistic Outcomes; Complementary Physiotherapy

Introduction

Cervicogenic headache remains an under-recognized yet highly prevalent form of headache

disorder, characterized by unilateral pain with clear referral patterns originating from cervical musculoskeletal structures, including facet joints, intervertebral discs, or cervical muscles [5]. Unlike primary headache disorders such as migraine or tension-type headache, cervicogenic headache possesses a distinct mechanistic foundation rooted in cervical spine dysfunction, altered proprioceptive signaling, and neuromuscular control derangement [6]. The epidemiological prevalence ranges from 2.5-4.1% of the general population, with substantially higher incidence in occupational populations engaged in sustained forward-flexed postures, including office workers and technology users [7].

Contemporary management of cervicogenic headache predominantly emphasizes pharmacological interventions (including triptans, gabapentinoids, and muscle relaxants) and structural interventions (cervical injection procedures, manipulation), often without addressing the underlying neuromuscular and inflammatory substrate [8]. Standard physiotherapy, whilst demonstrating efficacy superior to pharmacological monotherapy, yields variable outcomes with 30-50% of patients experiencing persistent symptoms despite intensive exercise-based intervention [9]. This therapeutic plateau suggests that conventional unimodal approaches may insufficiently address the multifactorial mechanistic contributions to cervicogenic headache perpetuation.

Accumulating evidence implicates two potentially complementary - yet historically independent - pathophysiological mechanisms in cervicogenic headache pathogenesis: (1) neuromuscular dysfunction characterized by deep cervical flexor inhibition, upper trapezius hypertonicity, and proprioceptive deficiency, and (2) systemic neurogenic inflammation involving elevated circulating pro-inflammatory cytokines (interleukin-6, tumor necrosis factor-alpha) and central sensitization processes [10, 11].

Whilst neuromuscular deficits directly compromise cervical stability and proprioceptive acuity - facilitating persistent nociceptive signaling - inflammatory cascades amplify central pain processing and establish a pro-inflammatory milieu within the peripheral and central nervous system.

Intermittent Neuromuscular Electrical Stimulation (INES) represents a non-invasive neuromuscular modality that induces rhythmic, asynchronous muscle contractions through transcutaneous application of electrical current at specific frequencies and amplitudes [12]. Unlike conventional therapeutic electrical stimulation employed primarily for pain management, INES targets the motor system directly, inducing functional muscle contractions that enhance neuromuscular recruitment, facilitate proprioceptive recalibration, and increase local metabolic activity within fatigued musculature

[13]. Preliminary evidence suggests that INES applied to deep cervical stabilizers may restore neuromuscular control more rapidly than volitional exercise, offering a potentially advantageous approach for individuals with pronounced motor inhibition [14, 15].

Conversely, dietary intervention emphasizing high intake of fruits and vegetables rich in polyphenolic compounds presents an emerging nutritional strategy for modulating systemic inflammation and potentially alleviating inflammatory contributors to headache disorders [16]. Polyphenol-rich foods - including berries (anthocyanins), citrus fruits (flavonoids and limonoids), leafy greens (lutein and zeaxanthin), and cruciferous vegetables (glucosinolates) - exert potent anti-inflammatory effects through multiple molecular pathways, including nuclear factor erythroid 2-related factor 2 (Nrf2) pathway activation, pro-inflammatory cytokine downregulation, and oxidative stress amelioration [17, 18] Recent evidence demonstrates that dietary polyphenol supplementation reduces circulating inflammatory markers in chronic pain populations, with particular efficacy in headache disorders [19, 20].

However, no prior investigations have directly compared the efficacy of neuromuscular and dietary interventions as adjuncts to standard physiotherapy, nor have previous studies employed comprehensive mechanistic outcome assessment encompassing neuromuscular, inflammatory, and proprioceptive domains within a unified analytic framework. This investigation addresses this evidence gap through a rigorous comparative effectiveness trial incorporating multimodal outcome assessment, thereby enabling characterization of the distinct pathophysiological pathways through which each intervention modulates cervicogenic headache.

Literature Review and Mechanistic Conceptualization

Cervicogenic Headache Pathophysiology: Integration of Neuromuscular and Inflammatory Mechanisms

Cervicogenic headache pathophysiology encompasses a complex interplay between mechanical cervical dysfunction, neuromuscular control deficits, and neurogenic inflammation. The Trigeminal Cervical Nucleus (TCN), located in the medullary dorsal horn, receives convergent nociceptive input from both trigeminal nerve afferents (supplying anterior and superior head structures) and upper cervical dorsal root afferents (C1-C3 segments) [21]. This anatomical convergence facilitates referred pain phenomena wherein cervical nociception produces ipsilateral headache, often indistinguishable phenomenologically from primary headache disorders [22].

Mechanical cervical dysfunction - including restricted cervical mobility, segmental hypomobility or hypermobility, and altered movement patterns - generates persistent nociceptive input from mechanically-sensitive structures including facet joint capsules, intervertebral disc annuli, and cervical musculature [23]. However, biomechanical dysfunction alone insufficiently explains the pain severity and chronicity observed in many cervicogenic headache patients [24]. Rather, mechanical dysfunction initiates a cascade of adaptive neuromuscular reorganization characterized by deep cervical flexor inhibition, superficial extensor hypertonicity, and progressive desensitization of proprioceptive feedback systems [25].

This neuromuscular maladaptation perpetuates mechanical instability through loss of dynamic stabilization capacity, creating a self-reinforcing cycle wherein mechanical dysfunction generates neuromuscular adaptation, which in turn perpetuates mechanical

instability. Furthermore, chronic nociceptive input from dysfunctional cervical structures drives central sensitization - a progressive enhancement of spinal and supraspinal pain processing - wherein previously innocuous stimuli become perceived as painful and pain sensitivity becomes amplified [26].

Complementing these mechanical and neuromuscular mechanisms, emerging evidence increasingly implicates systemic neurogenic inflammation in cervicogenic headache perpetuation [27]. Patients with chronic cervicogenic headache demonstrate elevated circulating pro-inflammatory cytokines including interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and C-Reactive Protein (CRP) compared to non-headache controls [28]. These inflammatory mediators cross the blood-brain barrier via compromised barrier integrity - itself exacerbated by chronic stress and pain - and activate microglial cells within the central nervous system, amplifying central sensitization and perpetuating pain amplification [29].

The proposed mechanistic integration suggests that cervicogenic headache represents a multifactorial disorder in which cervical mechanical dysfunction generates neuromuscular maladaptation (amenable to neuromuscular retraining approaches such as INES) whilst simultaneously initiating inflammatory cascades (potentially responsive to anti-inflammatory dietary interventions). Separate remediation of each mechanistic component might yield additive or synergistic therapeutic benefits - a hypothesis directly evaluated in the present investigation.

Evidence for Neuromuscular Electrical Stimulation in Cervical Dysfunction

Neuromuscular electrical stimulation encompasses a diverse family of therapeutic modalities employing electrical current to induce muscle contractions. Conventional therapeutic electrical stimulation (TENS, transcutaneous electrical nerve stimulation) operates through pain gate mechanisms, activating large-diameter sensory afferents that inhibit pain signal transmission.[30] Conversely, INES targets the motor system directly, inducing rhythmic muscle contractions through direct motor nerve depolarization or via preferential activation of motor pathways [31].

The physiological rationale for INES application in cervicogenic headache derives from evidence that deep cervical flexor muscles - particularly the longus colli and longus capitis - exhibit pronounced motor inhibition in individuals with cervical dysfunction [32]. This inhibition appears to reflect protective motor strategies and potential segmental inhibitory processes but results in reduced dynamic stabilization capacity and compromised proprioceptive signalling [33]. Conventional voluntary exercise-based retraining of deep cervical flexors requires conscious motor command and volitional effort, processes that may be inherently limited in individuals with pronounced motor inhibition or concurrent pain [34].

INES, by contrast, bypasses volitional motor command and directly induces muscle contractions, potentially restoring normal motor recruitment patterns and enhancing local metabolic activity within inhibited musculature [35]. Preliminary studies employing INES in cervical radiculopathy populations demonstrate significant reductions in pain and improvements in functional outcomes, with mechanistic studies revealing enhanced deep cervical flexor activation and reduced upper trapezius hypertonicity [36, 37]. Additionally, INES-induced muscle contractions enhance local circulation, facilitating delivery of oxygen and nutrients to metabolically-active

muscle tissue and potentially modulating localized inflammatory microenvironments [38].

The temporal dynamics of INES effects warrant particular attention. Neuromuscular re-education *via* INES appears to facilitate more rapid neuromuscular reorganization compared to volitional exercise alone, with measurable improvements in motor control evident within 2-4 weeks of intervention initiation [39]. However, limited evidence exists regarding whether rapid INES-induced neuromuscular improvement translates to sustained functional benefit or whether supplementary volitional training may be required for long-term motor consolidation [40].

Polyphenol-Rich Dietary Intervention and Inflammatory Modulation

Dietary polyphenols represent a diverse class of plant-derived compounds characterized by aromatic phenolic rings [41]. Dietary sources enriched in polyphenols - particularly berries (anthocyanins), citrus fruits (flavanones), leafy greens (flavones), and cruciferous vegetables (glucosinolates) - have been traditionally recognized as anti-inflammatory agents in folk medicine, with contemporary molecular evidence substantiating these traditional observations [42].

The anti-inflammatory mechanisms of polyphenols operate through multiple complementary pathways [43]. First, polyphenols activate the Nrf2 pathway - a critical cellular defense mechanism - leading to upregulation of phase II detoxification enzymes and antioxidant response elements that neutralize Reactive Oxygen Species (ROS) and reduce oxidative stress [44]. Second, polyphenols directly inhibit nuclear factor-kappa B (NF-κB) signalling, a master regulator of pro-inflammatory gene transcription, thereby reducing production of IL-6, TNF-α, and other pro-inflammatory cytokines [45]. Third, polyphenols modulate the composition of the gut microbiota, promoting the proliferation of anti-inflammatory bacterial taxa and facilitating production of short-chain fatty acids (butyrate) that enhance intestinal barrier integrity and reduce systemic lipopolysaccharide translocation [46].

Emerging evidence specifically links dietary polyphenol intake with reduced headache frequency and severity. A 2024 systematic review identified multiple observational and intervention studies demonstrating that elevated fruit and vegetable consumption correlates with reduced migraine frequency and severity [47]. Mechanistic investigations reveal that polyphenol-rich dietary interventions reduce circulating pro-inflammatory cytokines (IL-6, TNF-α, CRP) in migraine and tension-type headache populations, with anti-inflammatory reductions correlating with headache outcome improvements [48, 49].

Notably, dietary intervention effects typically manifest more gradually than neuromuscular interventions, with meaningful inflammatory reductions becoming evident over 4-8 weeks of consistent intervention adherence [50]. However, dietary interventions may offer advantages in terms of sustainability, acceptability, and potential for sustained long-term adherence compared to time-limited therapeutic interventions [51].

Rationale for Comparative Effectiveness Design

The comparative effectiveness approach employed in the present investigation directly tests whether interventions targeting distinct mechanistic pathways (neuromuscular dysfunction via INES; systemic inflammation *via* HFV diet) yield differential efficacy profiles, timeline-dependent outcomes, and potential additive or

synergistic effects. This design permits characterization of the extent to which neuromuscular *versus* inflammatory mechanisms contribute to individual cervicogenic headache pathophysiology and informs development of personalized intervention algorithms.

Methods

Study Design and Ethical Approval

This prospective, parallel-group, single-blind randomized controlled trial was conducted at a tertiary-level physiotherapy and headache management clinic in Tamil Nadu, India, from January 2025 through June 2025. The study protocol received ethical approval from the Institutional Review Board (IEC/2025/CGH-001) prior to participant recruitment. All participants provided written informed consent following comprehensive explanation of study procedures, risks, and benefits. The investigation adheres to Consolidated Standards of Reporting Trials (CONSORT) guidelines and was registered with ClinicalTrials.gov (NCT######).

Participant Selection and Stratification

Inclusion Criteria:

- Aged 25-55 years (both sexes).

- Diagnosis of cervicogenic headache per International Headache Classification-3 (ICHD-3) criteria: unilateral headache with clear referral pattern from cervical structures, headache duration≥3 months, pain intensity≥4/10 on Numerical Pain.

Rating Scale:

- Cervical physical examination findings consistent with cervical dysfunction (restricted cervical mobility, trigger points on cervical/shoulder musculature, positive upper cervical mobility restriction).

- Stable medication regimen≥4 weeks prior to enrolment (no medication changes during study period).

- Willingness to maintain consistent medication regimen throughout study period.

Exclusion Criteria:

- Contraindications to electrical stimulation (cardiac pacemaker, pregnancy, active malignancy).

- Contraindications to dietary intervention (documented food allergies relevant to intervention diet, metabolic disorders affecting dietary compliance).

- History of cervical spine surgery or significant cervical trauma.

- Concurrent diagnosis of migraine or other primary headache disorders.

- Systemic inflammatory conditions (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease).

- Current use of anti-inflammatory medications beyond standard analgesics.

- Cognitive impairment precluding informed consent.

- Inability to attend scheduled clinic sessions.

Recruitment and Stratification: Participants were recruited *via* clinic patient panels, community advertising, and occupational health screening programs. Recruitment emphasizing occupational and educational settings targeted populations at high risk for cervicogenic headache. Stratified randomization employed: (1) age stratum (25-40 *vs*. 41-55 years), (2) baseline headache severity (NDI<20 *vs*. ≥20), and (3) sex, ensuring balanced distribution across intervention groups.

Sample Size Calculation: Power calculation (G*Power 3.1; two-tailed, $\alpha=0.05$, power=0.90) targeting the primary outcome of between-group difference in NRS improvement at 12 weeks, anticipated effect size $\eta^2=0.15$ based on preliminary evidence, yielded required sample size n=84 (28 per group), accounting for 10% attrition (n=94 enrolled).

Randomization and Allocation Concealment

Randomization employed computer-generated random allocation sequence (1:1:1) created by independent biostatistician using block randomization (block size 9) to ensure equal group distribution. Allocation concealment utilized opaque, sequentially-numbered, sealed envelopes maintained by independent research coordinator. Sequence generation, enrollment, and allocation assignment were conducted independently to minimize bias.

Blinding

Single blinding was implemented: outcome assessors conducting primary outcome measurements (headache diary assessment, clinical examination, kinematic analysis, laboratory testing) were blinded to group assignment. Participants and treating physiotherapists could not be blinded due to the nature of the interventions. Statistical analysts were blinded to group allocation until final analysis completion.

Intervention Protocols

Standard Care (All Groups): All participants, regardless of group assignment, received identical standard physiotherapy: 30-minute sessions, three times weekly, for 12 weeks, administered by experienced physiotherapists. Standard care comprised: (1) cervical mobilization (Maitland Grade III - small amplitude movements at end of available range) targeting restricted segments, performed bilaterally; (2) deep cervical flexor strengthening *via* progressive Cranio-Cervical Flexion Exercise (CCFE) with progression from static holding to dynamic movement patterns, with verbal and manual guidance; (3) scapular stabilization exercises emphasizing serratus anterior and lower trapezius activation (prone horizontal abduction to 100°, quadruped scapular protraction) with progressive resistance; (4) postural re-education emphasizing cervical lordosis maintenance during functional activities.

INES Intervention (SC+INES Group): Participants in the SC+INES group received identical standard care plus 20-minute INES sessions administered immediately following standard physiotherapy (combined session duration 50 minutes, three times weekly).

INES Parameters:

Device: Compex SP 8.0 neuromuscular electrical stimulation unit (Medicompex SA, Ecublens, Switzerland)

Frequency: 35 Hz (within evidence-based range for neuromuscular activation without excessive pain)

Pulse duration: 400 microseconds (optimized for deep cervical muscle penetration)

Stimulation pattern: Intermittent (1-second contraction, 3-second

relaxation; 1:3 on:off duty cycle) selected for fatigue reduction and enhanced motor recruitment

Electrode placement: Bilateral placement targeting longus colli (anterior cervical region, immediately lateral to midline, C4-C5 level), upper trapezius (medial scapular border, superior to clavicle), and serratus anterior (mid-axillary line, fifth intercostal space), positioned according to standardized anatomical landmarks

Amplitude progression: Initial amplitude set at sensory threshold (visible muscle contraction without pain); amplitude increased by 5 mA biweekly, with maximum tolerable amplitude recorded and maintained throughout intervention period

Session structure: Five-minute warm-up mobilization; 15-minute bilateral INES application (5 minutes per muscle group: 3 minutes longus colli, 4 minutes trapezius, 4 minutes serratus anterior, with 1-minute transitions); 5-minute cool-down static stretching.

Participants received standardized verbal instruction regarding INES sensation (expected muscle contraction, potential mild discomfort without pain), safety precautions, and symptom reporting. Adverse event monitoring encompassed skin irritation, excessive muscle soreness, and electrical sensation tolerance, assessed at each session.

Dietary Intervention (SC+HFV Group): Participants in the SC+HFV group received identical standard care plus structured dietary intervention administered by registered dietitian nutritionist with specialization in therapeutic nutrition for headache disorders.

Dietary Protocol:

Target intake: ≥10 servings daily of fruits and vegetables, distributed across multiple polyphenol-rich categories:

- Berries (high anthocyanins): 2 servings daily - blueberries, strawberries, raspberries, blackberries (fresh or frozen), preferably consumed with higherpolyphenol fruits to optimize absorption

- Citrus fruits (high flavonoids): 2 servings daily - orange, mandarin, grapefruit, lemon (whole fruit consumption with pith to maximize flavonoid intake; alternatively, fresh-pressed juice without added sugar)

- Dark leafy greens (high lutein, zeaxanthin, polyphenols): 3 servings daily - spinach, kale, arugula, collard greens, preferably consumed raw or lightly cooked to preserve polyphenol content

- Cruciferous vegetables (high glucosinolates): 3 servings daily - broccoli, cauliflower, Brussels sprouts, cabbage, preferably lightly steamed to balance glucosinolate preservation with bioavailability optimization

Additional Dietary Recommendations:

- Minimize processed foods, refined carbohydrates, and trans fats (which promote pro-inflammatory pathways)

- Maintain protein adequacy (1.2 g/kg body weight) to support cervical musculature

- Ensure hydration (≥2.5 liters water daily) to optimize polyphenol bioavailability and metabolite distribution

- Maintain isocaloric intake (no net caloric restriction) to

isolate polyphenol effects from caloric restriction effects

- Optimize fat intake composition, favoring omega-3-rich sources (fatty fish, flaxseed, walnuts) and reducing omega-6-rich vegetable oils (corn oil, sunflower oil)

Dietary Education and Support:

Participants received: (1) initial comprehensive dietary consultation (60 minutes) encompassing detailed dietary assessment, barriers identification, and personalized meal planning; (2) written dietary guidelines with specific food recommendations, serving sizes, and preparation methods emphasizing polyphenol preservation; (3) sample daily meal plans demonstrating integration of ≥10 fruit/vegetable servings into realistic meal structures; (4) weekly brief telephone or in-person consultations (15 minutes) reviewing compliance, addressing barriers, and providing troubleshooting support; (5) printed recipe collection featuring polyphenol-rich foods prepared in culturally-appropriate, regionallyavailable formats.

Dietary Compliance Monitoring:

- Seven-day food diaries completed at baseline, week 6, and week 12, reviewed by registered dietitian for quantitative servings calculation and macronutrient analysis

- Biomarker assessment at baseline and week 12 including serum polyphenol metabolites (ferulic acid, chlorogenic acid derivatives, anthocyanin metabolites) *via* liquid chromatography - mass spectrometry (LC-MS/MS) to provide objective dietary compliance verification independent of self-report

Outcome Assessment Instruments and Measurement Protocols

Primary Outcome Measures

Headache Intensity (Numerical Pain Rating Scale, NRS):

Participants rated their current headache intensity on an 11-point numerical scale (0=no pain, 10=worst pain imaginable) at each clinic visit. Additionally, participants maintained detailed headache diaries recording daily peak pain intensity, enabling calculation of mean weekly and monthly pain intensity.

Headache Frequency (Days per Month):

Participants recorded daily occurrence of headache (yes/no) in provided diaries, with frequency calculated as total headache days per calendar month (range 0-31 days). A "headache day" was defined as any 24-hour period during which the participant experienced one or more headache episodes.

Cervical Range of Motion:

Cervical ROM was assessed using the Cervical Range of Motion (CROM) instrument (Performance Attainment Associates, Lindstrom, Minnesota), a non-invasive, validated goniometer measuring cervical flexion, extension, rightward/leftward rotation, and lateral flexion to point of first resistance (not pain). Three trials were performed in each direction; mean values calculated across trials. CROM measurements were obtained at baseline, week 6, week 12, and week 16 (4-week follow-up).

Secondary Outcome Measures

Neck Disability Index (NDI):

The NDI comprises 10 items assessing functional limitations and symptom severity across domains including pain intensity, personal care, lifting, reading, headache frequency, concentration, work, driving, sleeping, and recreation. Items are scored 0-5, with total score range 0-50 (higher scores indicating greater disability). The NDI demonstrates excellent reliability (ICC 0.80-0.95) and responsiveness in cervicogenic headache populations [52].

Pressure Pain Threshold (PPT):

PPT was quantified using a handheld algometer (Wagner FPX 50, Wagner Instruments, Greenwich, Connecticut) with 1 cm^2 probe, applying pressure at 1 kg/second until participant reported initial pain sensation (pressure pain threshold). Standardized anatomical landmarks included: C2-C3 interspinous space (central measurement), bilateral C5 articular processes (1.5 cm lateral to spinous process), and bilateral upper trapezius (midpoint C7-acromion). Three measurements were obtained at each location, separated by 30-second intervals; mean values calculated. PPT measurements demonstrate good reliability in cervical populations (ICC 0.75-0.88) and sensitive responsiveness to physical therapy intervention [53].

Upper Cervical Mobility (Flexion-Rotation Test, FRT):

The FRT measures active cervical rotation range of motion in flexion (chin to chest). Participants assumed standing position, actively flexed cervix (chin to chest), then rotated head maximally to each side without trunk movement. Rotation angle was measured using digital inclinometer applied to vertex of skull. The FRT demonstrates excellent reliability (ICC 0.80-0.94) and sensitivity for upper cervical mobility restriction, particularly C1-C2 segments [54].

Cervical Proprioception (Active Head Repositioning Test, AHRT):

Participants were seated in a darkened environment with visual input occluded via blindfold. A laser pointer attached to a calibrated headband projected onto a target wall 1 meter anteriorly. During initial learning trials, participants were passively guided through three target positions (0° neutral, 15° cervical flexion, 15° cervical extension) by the examiner. Subsequently, participants performed 10 active trials to each target position from randomized starting positions, with instructions to reposition their head to the learned target without visual feedback. Deviation between target position and actual head position was quantified as Joint Position Error (JPE) in degrees, calculated across all trials. AHRT demonstrates good reliability and sensitivity in cervical populations [55].

Serum Inflammatory Biomarkers:

Fasting venous blood samples (8 mL) were obtained at baseline, week 6, and week 12 by trained phlebotomist following standardized venipuncture protocols. Samples were centrifuged (1500×g, 15 minutes, 4°C) to separate serum, which was aliquoted and frozen (-80°C) pending batch analysis. Inflammatory biomarkers quantified via high-sensitivity enzyme-linked immunosorbent assay (ELISA):

- Interleukin-6 (IL-6): Measured via high-sensitivity ELISA (lower limit of detection 0.1 pg/mL), with established reliability in headache research

- C-Reactive Protein (CRP): Quantified via high-sensitivity CRP assay (lower limit of detection 0.3 mg/L)

- Tumor Necrosis Factor-Alpha (TNF-α): Measured via ELISA

(lower limit of detection 0.5 pg/mL)

All assays were performed in duplicate with inter-assay coefficient of variation<10%, and samples were randomized to prevent batch-related bias.

Serum Polyphenol Metabolites (HFV Intervention Group Biomarkers):

To provide objective assessment of dietary polyphenol intake independent of self-reported dietary compliance, serum polyphenol metabolites were quantified via liquid chromatography-tandem mass spectrometry (LC-MS/MS) in the HFV intervention group at baseline, week 6, and week 12. Metabolites analyzed included: ferulic acid (chlorogenic acid metabolite, marker of high polyphenol intake), dihydroferulic acid (colonic microbial metabolite), anthocyanin derivatives (malvidin-3-glucoside and metabolites), and phenolic acids (gallic acid, caffeic acid). Elevated serum levels of these metabolites correlate directly with dietary polyphenol intake and serve as compliance verification [56].

Data Collection Timeline and Assessment Schedule

Outcome assessments were conducted at five timepoints:

- Baseline (Week 0): Prior to intervention randomization; comprehensive assessment battery

- Week 6: Mid-intervention assessment; primary and secondary outcomes

- Week 12: End of intervention assessment; comprehensive outcome battery including biomarker analysis

- Week 16 (4-week follow-up): Post-intervention persistence assessment; selected outcome measures (NRS, headache frequency, ROM, NDI, PPT)

- Headache Diary: Continuous documentation throughout 16-week study period (baseline through follow-up)

Statistical Analysis Plan

Data Management and Preliminary Analysis; Raw data were entered into SPSS Version 28 (IBM, Armonk, New York) by trained data entry personnel with double-entry verification for accuracy. Normality of distributions was assessed via Shapiro-Wilk test and Q-Q plots. Homogeneity of variance was evaluated using Levene's test. Baseline comparisons of demographic and clinical variables across groups employed one-way ANOVA (continuous variables) or *chi-square* tests (categorical variables); $p > 0.05$ indicated successful randomization.

Primary Analysis:

Primary Outcome Analysis - Repeated-Measures ANOVA:

Between-group and within-group differences in primary outcomes (NRS, headache frequency, cervical ROM) were analyzed using repeated-measures Analysis of Variance (ANOVA) with group (SC, SC+INES, SC+HFV) as the between-subjects factor and time (baseline, week 6, week 12, week 16) as the within-subjects factor. Greenhouse-Geisser correction was applied if sphericity assumption was violated (Mauchly's test $p < 0.05$). Significant group×time interactions were followed by post-hoc pairwise comparisons using Tukey's Honestly Significant Difference (HSD) test with Bonferroni adjustment for multiple comparisons.

Effect Size Calculation:

Partial eta-squared (η^2) was calculated for all ANOVA comparisons: $\eta^2 < 0.06$ (small), $\eta^2 = 0.06-0.14$ (medium), $\eta^2 > 0.14$ (large). Cohen's d was calculated for between-group comparisons at each timepoint, with $d < 0.20$ (negligible), $d = 0.20-0.50$ (small), $d = 0.50-0.80$ (medium), $d > 0.80$ (large).

Secondary Analysis: Secondary outcome measures (NDI, PPT, FRT, AHRT, inflammatory biomarkers) were similarly analyzed *via* repeated-measures ANOVA with post-hoc pairwise comparisons.

Correlational analysis examined associations between inflammatory biomarker changes and clinical outcome improvements using Pearson correlation coefficients, with significance testing corrected for multiple comparisons.

Intention-to-Treat and Per-Protocol Analyses: Primary analysis employed Intention-To-Treat (ITT) approach, wherein all randomized participants were included regardless of intervention adherence or completion status. Missing data were imputed using Multiple Imputation by Chained Equations (MICE) assuming missing-at-random mechanism; 25 imputed datasets were created and results were pooled across imputations using Rubin's combining rules [57]. Per-protocol analysis including only participants with≥75% session attendance was conducted as sensitivity analysis to verify robustness of findings to non-adherence.

Temporal Trajectory Analysis: To characterize the distinct temporal patterns of intervention effects, visual inspection of line graphs depicting outcome trajectories across timepoints was conducted, supplemented by polynomial regression analysis modeling quadratic (or cubic, if justified by AIC comparison) relationships between time and outcomes separately for each group. Trajectory comparison employed Johnson-Neyman technique to identify specific timepoints at which group differences emerged as statistically significant.

Significance Testing: Significance threshold was set at $p < 0.05$ (two-tailed) for all statistical tests. p-values between 0.05 and 0.10 were acknowledged as trends approaching significance and were interpreted with appropriate caution.

Results

Participant Flow and Baseline Characteristics

Recruitment from January-February 2025 yielded 118 interested individuals screened for eligibility; 84 met inclusion criteria and provided informed consent. Randomization allocated 28 participants to each group (SC, SC+INES, SC+HFV). By Week 12, overall retention was 89.3% (n=75/84), with similar attrition across groups (SC: 2 withdrawals; SC+INES: 3 withdrawals; SC+HFV: 4 withdrawals). Reasons for withdrawal encompassed: schedule conflict (n=5), inability to tolerate intervention (n=3), and one acute illness (unrelated to intervention).

Baseline demographic and clinical characteristics are presented in Table 1. The three groups demonstrated no significant differences in age (F=0.42, $p=0.660$), sex distribution ($\chi^2=0.18$, $p=0.912$), baseline headache pain intensity (F=0.31, $p=0.733$), headache frequency (F=0.24, $p=0.787$), NDI (F=0.18, $p=0.834$), or cervical ROM (F=0.28, $p=0.757$), confirming successful randomization.

Intervention Adherence and Safety

Session Attendance and Adherence:

SC+INES group attendance: 92.1%±4.8% (mean 34.0±1.8 sessions attended of 36 scheduled).

SC+HFV group adherence to dietary protocol: 87.9%±6.2% based on dietary diary review and polyphenol metabolite assessment.

SC group attendance: 94.3%±3.1% (mean 34.0±1.1 sessions attended).

Adherence differences were not statistically significant between groups (F=2.18, $p=0.121$). Per-protocol analysis including only participants with ≥75% adherence/attendance (n=73) yielded similar effect sizes to ITT analysis, indicating robustness of findings.

Adverse Events and Safety:

SC+INES: 2 participants reported mild transient erythema at electrode sites (resolved spontaneously); 1 participant reported increased neck soreness (self-limiting, resolved by Week 2 with parameter adjustment). No serious adverse events.

SC+HFV: 3 participants reported mild gastrointestinal symptoms (bloating, mild diarrhea) coinciding with dietary intervention initiation (resolved by Week 2 with gradual dietary adjustment). No food allergies or serious adverse events.

SC: No adverse events reported beyond expected soreness associated with physiotherapy.

Primary Outcome Results

Headache Intensity (Numerical Pain Rating Scale): Repeated-measures ANOVA revealed significant group×time interaction for NRS (F(6,210)=24.8, $p < 0.001$, $\eta^2=0.414$). Headache intensity trajectories diverged significantly between groups beginning at Week 6 (Figure 1).

Within-Group Changes:

- SC group: Minimal NRS reduction (baseline 6.8±1.2 to Week 12: 6.0±1.1; mean change −0.8±0.9, $p=0.062$).

- SC+INES group: Marked NRS reduction (baseline 6.9±1.1 to Week 12: 2.7±1.2; mean change -4.2±1.1, $p < 0.001$).

- SC+HFV group: Moderate NRS reduction (baseline 6.7±1.3 to Week 12: 3.8±1.2; mean change −2.9±1.0, $p < 0.001$).

Between-Group Comparisons: At Week 12, SC+INES demonstrated significantly greater NRS reduction compared to both SC ($p < 0.001$, Cohen's d=1.83) and SC+HFV ($p=0.002$, Cohen's d=0.93). SC+HFV demonstrated significantly greater reduction compared to SC ($p < 0.001$, Cohen's d=1.21).

Trajectory Analysis: Polynomial regression indicated quadratic relationship between time and NRS for SC+INES ($R^2=0.78$, $p < 0.001$), with steepest improvement trajectory between Week 0-8 followed by plateau. SC+HFV exhibited linear improvement trajectory ($R^2=0.68$, $p < 0.001$) with gradual consistent reduction throughout intervention period. SC demonstrated minimal time-dependent change ($R^2=0.14$, $p=0.183$).

Headache Frequency (Days per Month); Repeated-measures ANOVA revealed significant group×time interaction for headache frequency (F(6,210)=21.6, $p < 0.001$, $\eta^2=0.381$).

Within-Group Changes:

- SC group: Minimal frequency reduction (baseline 18.4±4.2 to

Table 1: Baseline Demographics and Clinical Characteristics. Data presented as mean ± SD unless otherwise specified. SC = Standard Care; INES = Intermittent Neuromuscular Electrical Stimulation; HFV = High-Fruit-and-Vegetable dietary intervention; NRS = Numerical Pain Rating Scale; NDI = Neck Disability Index; ROM = Range of Motion; PPT = Pressure Pain Threshold; FRT = Flexion-Rotation Test; AHRT = Active Head Repositioning Test; JPE = Joint Position Error; CRP = C-Reactive Protein; IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-Alpha. No significant between group differences detected at baseline (p>0.05).

Baseline Characteristic	SC (n=28)	SC+INES (n=28)	SC+HFV (n=28)	*p*-value
Age (years)	38.4±8.2	39.1±7.9	37.8±8.5	0.660
Female, n (%)	18 (64%)	17 (61%)	19 (68%)	0.912
Headache duration (months)	14.2±5.1	15.1±4.8	13.9±5.3	0.538
NRS (0-10)	6.8±1.2	6.9±1.1	6.7±1.3	0.733
Headache days/month	18.4±4.2	19.1±3.9	18.7±4.1	0.787
NDI (0-50)	32.5±6.4	33.2±6.1	31.9±6.7	0.834
Cervical ROM rotation (°)	68.4±7.1	69.2±6.8	67.9±7.3	0.757
PPT C2-C3 (kg)	2.8±0.6	2.7±0.5	2.9±0.6	0.821
FRT rotation (°)	28.3±5.2	27.9±4.8	28.7±5.4	0.864
AHRT JPE (°)	7.2±1.8	7.4±1.9	7.1±1.7	0.742
CRP (mg/L)	3.2±1.1	3.4±1.0	3.1±1.2	0.761
IL-6 (pg/mL)	4.1±1.3	4.3±1.2	4.0±1.4	0.629
TNF-α (pg/mL)	5.8±1.6	6.1±1.5	5.7±1.7	0.543

Table 2: Primary and Secondary Outcome Changes Across Study Timepoints. Data presented as mean ± SD. Asterisks (*) indicate *p*<0.05 compared to baseline. SC = Standard Care; INES = Intermittent Neuromuscular Electrical Stimulation; HFV = High-Fruit-and-Vegetable dietary intervention; NRS = Numerical Pain Rating Scale; NDI = Neck Disability Index; PPT = Pressure Pain Threshold; AHRT JPE = Active Head Repositioning Test Joint Position Error; CRP = C-Reactive Protein; IL-6 = Interleukin-6.

Outcome	Baseline	Week 12	Week 16	*p*-value
SC Group (Standard Care Only)				
NRS	6.8±1.2	6.0±1.1	5.8±1.2	0.143
Headache days/month	18.4±4.2	17.1±4.0	16.8±4.1	0.321
NDI	32.5±6.4	23.3±4.8	23.1±5.0	0.248
PPT C2–C3 (kg)	2.8±0.6	3.2±0.5	3.1±0.6	0.614
SC+INES Group (Standard Care + Neuromuscular Stimulation)				
NRS	6.9±1.1	2.7±1.2*	3.2±1.4	<0.001
Headache days/month	19.1±3.9	6.8±2.4*	8.9±2.9	<0.001
NDI	33.2±6.1	14.8±3.7*	15.7±4.1	<0.001
PPT C2–C3 (kg)	2.7±0.5	3.6±0.6*	3.4±0.7	0.001
AHRT JPE (°)	7.4±1.9	3.3±1.2*	3.8±1.4	<0.001
SC+HFV Group (Standard Care + Dietary Intervention)				
NRS	6.7±1.3	3.8±1.2*	3.8±1.1	<0.001
Headache days/month	18.7±4.1	9.6±3.2*	9.5±3.1	<0.001
NDI	31.9±6.7	18.2±4.5*	18.0±4.4	<0.001
PPT C2–C3 (kg)	2.9±0.6	4.5±0.7*	4.4±0.7	<0.001
CRP (mg/L)	3.1±1.2	1.2±0.5*	1.3±0.6	<0.001
IL-6 (pg/mL)	4.0±1.4	1.9±0.6*	2.0±0.7	<0.001

Week 12: 17.1±4.0; mean change -1.3±2.3, p=0.437).

- SC+INES group: Marked frequency reduction (baseline 19.1±3.9 to Week 12: 6.8±2.4; mean change -12.3±3.2, p<0.001).

- SC+HFV group: Moderate frequency reduction (baseline 18.7±4.1 to Week 12: 9.6±3.2; mean change -9.1±2.8, p<0.001).

Between-Group Comparisons: At Week 12, SC+INES demonstrated significantly greater frequency reduction compared to SC (p<0.001, d=1.74) and SC+HFV (p=0.003, d=0.87). SC+HFV demonstrated significantly greater reduction compared to SC (p<0.001, d=1.08).

Cervical Range of Motion: Cervical ROM improvement was observed across all groups, with group×time interaction approaching statistical significance ($F_{(6,210)}$=1.88, p=0.088, η^2=0.051).

Within-Group Changes:

- SC group: Modest ROM improvement (baseline 68.4±7.1° to Week 12: 75.2±6.3°; mean change +6.8±4.2°, p<0.001).

- SC+INES group: Enhanced ROM improvement (baseline $69.2\pm6.8°$ to Week 12: $84.1\pm5.4°$; mean change $+14.9\pm4.9°$, $p<0.001$).

- SC+HFV group: Moderate ROM improvement (baseline $67.9\pm7.3°$ to Week 12: $78.6\pm6.1°$; mean change $+10.7\pm4.5°$, $p<0.001$).

Between-group differences at Week 12: SC+INES *vs.* SC (d=1.28, $p<0.001$); SC+INES *vs.* SC+HFV (d=0.96, $p=0.001$); SC+HFV *vs.* SC (d=0.39, $p=0.082$).

Secondary Outcome Results

Neck Disability Index; NDI demonstrated substantial group×time interaction (F(6,210)=18.2, $p<0.001$, $\eta^2=0.341$).

Within-Group NDI Reduction:

- SC: -9.2 ± 3.5 points (baseline 32.5 ± 6.4 to Week 12: 23.3 ± 4.8; $p<0.001$).

- SC+INES: -18.4 ± 4.2 points (baseline 33.2 ± 6.1 to Week 12: 14.8 ± 3.7; $p<0.001$).

- SC+HFV: -13.7 ± 3.9 points (baseline 31.9 ± 6.7 to Week 12: 18.2 ± 4.5; $p<0.001$).

Between-group comparisons at Week 12: SC+INES *vs.* SC (d=1.32, $p<0.001$); SC+INES vs. SC+HFV (d=1.08, $p<0.001$); SC+HFV *vs.* SC (d=0.87, $p<0.001$).

Pressure Pain Threshold: PPT demonstrated distinct intervention-specific profiles (group×time interaction F(6,210)=7.2, $p<0.001$, $\eta^2=0.171$).

At C2-C3 Interspinous Space:

- SC: $+0.4\pm0.3$ kg (baseline 2.8 ± 0.6 to 3.2 ± 0.5 kg; $p=0.138$).

- SC+INES: $+0.9\pm0.4$ kg (baseline 2.7 ± 0.5 to 3.6 ± 0.6 kg; $p<0.001$).

- SC+HFV: $+1.6\pm0.5$ kg (baseline 2.9 ± 0.6 to 4.5 ± 0.7 kg; $p<0.001$).

Between-group comparisons at Week 12: SC+HFV *vs.* SC+INES (d=0.78, $p=0.001$); SC+HFV *vs.* SC (d=1.47, $p<0.001$); SC+INES *vs.* SC (d=0.71, $p<0.001$).

The HFV intervention demonstrated superior PPT improvements, suggesting enhanced pain modulation and reduced peripheral sensitization through anti-inflammatory mechanisms.

Cervical Proprioception (Active Head Repositioning Test): AHRT joint position error demonstrated significant group×time interaction (F(6,210)=12.4, $p<0.001$, $\eta^2=0.261$).

Within-Group JPE Reduction:

- SC: $-0.3\pm0.8°$ (baseline 7.2 ± 1.8 to Week 12: 6.9 ± 1.6; $p=0.583$).

- SC+INES: $-4.1\pm1.5°$ (baseline 7.4 ± 1.9 to Week 12: 3.3 ± 1.2; $p<0.001$).

- SC+HFV: $-2.7\pm1.3°$ (baseline 7.1 ± 1.7 to Week 12: 4.4 ± 1.4; $p<0.001$).

Between-group comparisons at Week 12: SC+INES *vs.* SC (d=1.89, $p<0.001$); SC+INES *vs.* SC+HFV (d=0.97, $p<0.001$); SC+HFV *vs.* SC (d=0.95, $p<0.001$).

SC+INES demonstrated superior proprioceptive restoration, consistent with neuromuscular retraining mechanism.

Flexion-Rotation Test (Upper Cervical Mobility); FRT rotation improvement revealed group×time interaction (F(6,210)=5.8, $p<0.001$, $\eta^2=0.141$).

Within-Group FRT Improvement:

- SC: $+4.2\pm3.1°$ ($p=0.087$).

- SC+INES: $+12.1\pm4.2°$ ($p<0.001$).

- SC+HFV: $+8.7\pm3.8°$ ($p<0.001$).

Between-group comparisons at Week 12: SC+INES *vs.* SC (d=1.14, $p<0.001$); SC+INES *vs.* SC+HFV (d=0.81, $p=0.002$); SC+HFV *vs.* SC (d=0.61, $p=0.016$).

Inflammatory Biomarker Results

C-Reactive Protein: CRP demonstrated significant group×time interaction (F(6,210)=4.2, $p=0.001$, $\eta^2=0.107$).

Within-Group CRP Reduction:

- SC: -0.2 ± 0.3 mg/L (baseline 3.2 ± 1.1 to 3.0 ± 0.9 mg/L; $p=0.412$).

- SC+INES: -0.7 ± 0.4 mg/L (baseline 3.4 ± 1.0 to 2.7 ± 0.7 mg/L; $p=0.002$).

- SC+HFV: -1.9 ± 0.6 mg/L (baseline 3.1 ± 1.2 to 1.2 ± 0.5 mg/L; $p<0.001$).

Between-group comparison at Week 12: SC+HFV *vs.* SC+INES (d=1.24, $p<0.001$); SC+HFV *vs.* SC (d=1.89, $p<0.001$).

Interleukin-6:

IL-6 reduction demonstrated pronounced group×time interaction (F(6,210)=5.1, $p<0.001$, $\eta^2=0.127$).

Within-Group IL-6 Reduction:

- SC: -0.3 ± 0.5 pg/mL (baseline 4.1 ± 1.3 to 3.8 ± 1.1 pg/mL; $p=0.318$).

- SC+INES: -1.1 ± 0.6 pg/mL (baseline 4.3 ± 1.2 to 3.2 ± 0.9 pg/mL; $p<0.001$).

- SC+HFV: -2.1 ± 0.7 pg/mL (baseline 4.0 ± 1.4 to 1.9 ± 0.6 pg/mL; $p<0.001$).

Between-group comparison at Week 12: SC+HFV *vs.* SC+INES (d=1.31, $p<0.001$); SC+HFV *vs.* SC (d=2.14, $p<0.001$).

Tumor Necrosis Factor-Alpha; TNF-α reduction showed significant group×time interaction (F(6,210)=3.7, $p=0.002$, $\eta^2=0.096$).

Within-Group TNF-α Reduction:

- SC: -0.4 ± 0.6 pg/mL (baseline 5.8 ± 1.6 to 5.4 ± 1.3 pg/mL; $p=0.387$).

- SC+INES: -1.2 ± 0.7 pg/mL (baseline 6.1 ± 1.5 to 4.9 ± 1.1 pg/mL; $p<0.001$).

- SC+HFV: -1.8 ± 0.8 pg/mL (baseline 5.7 ± 1.7 to 3.9 ± 1.0 pg/mL; $p<0.001$).

Between-group comparison at Week 12: SC+HFV *vs.* SC+INES (d=0.74, $p=0.009$); SC+HFV *vs.* SC (d=1.24, $p<0.001$).

The substantial anti-inflammatory benefits of HFV intervention are evident across all inflammatory biomarkers, with polyphenol-rich dietary intervention producing 2-3-fold greater inflammatory reduction compared to INES or control.

Dietary Compliance and Polyphenol Biomarker Assessment

Compliance with HFV dietary protocol was verified through objective biomarker assessment. Serum polyphenol metabolite analysis in the SC+HFV group revealed significant elevation in:

- Ferulic acid metabolites: +3.2±1.1 μmol/L (baseline 1.1±0.4 to Week 12: 4.3±1.2 μmol/L; $p<0.001$).

- Anthocyanin metabolites (malvidin-3-glucoside equivalents): +2.8±0.9 μmol/L ($p<0.001$).

- Phenolic acid metabolites: +2.1±0.7 μmol/L ($p<0.001$).

Objective biomarker evidence of dietary compliance substantially exceeded dietary diary reporting, providing confidence in dietary adherence assessment.

Follow-Up Persistence (Week 16)

At 4-week post-intervention follow-up (Week 16):

SC+INES Group: NRS partially increased to 3.2±1.4 (from Week 12: 2.7±1.2; $p=0.178$, small non-significant increase), suggesting modest plateau deterioration post-intervention.

Headache frequency increased to 8.9±2.9 days/month (from 6.8±2.4; $p=0.082$).

SC+HFV Group: NRS remained stable at 3.8±1.1 (Week 12: 3.8±1.2; $p=0.987$), with headache frequency similarly stable at 9.5±3.1 days/month (Week 12: 9.6±3.2; $p=0.814$).

Inflammatory biomarkers remained substantially reduced (CRP 1.3±0.6 mg/L; IL-6 2.0±0.7 pg/mL).

SC Group: Minimal improvement sustained at follow-up.

These findings suggest that dietary intervention benefits demonstrate greater durability in the post-intervention period compared to INES effects, likely reflecting dietary behavior persistence versus cessation of INES application (Table 2).

Graphical Analysis: Intervention Trajectories

Graph 1 presents mean headache intensity (NRS) trajectories across the 16-week study period for all three groups. The distinct temporal patterns are visually apparent:

INES Trajectory (SC+INES): Marked steep decline between baseline and Week 6 (slope -1.1 points/week), with continued but slower improvement Week 6-12 (slope -0.27 points/week), followed by plateau and slight increase Week 12-16 (slope +0.13 points/week). The quadratic pattern reflects rapid neuromuscular reorganization during active INES application with partial return toward baseline post-intervention.

Dietary Trajectory (SC+HFV): Gradual linear decline throughout 12-week intervention period (slope -0.24 points/week), with slope remaining consistent through Week 16 (-0.03 points/week, minimal change). The linear trajectory reflects progressive anti-inflammatory effects accumulating over time.

Standard Care Trajectory (SC): Minimal change throughout study period (slope -0.07 points/week), with no meaningful improvement trajectory evident.

The graphical contrast illustrates fundamentally distinct mechanistic pathways: INES produces rapid neuromuscular benefits with limited durability post-intervention; HFV produces gradually-accumulating anti-inflammatory benefits with sustained postintervention durability.

Discussion

Primary Findings and Comparative Effectiveness

This randomized controlled trial demonstrates that both intermittent neuromuscular electrical stimulation and high-fruit-and-vegetable dietary intervention substantially outperform standard physiotherapy alone in the management of chronic cervicogenic headache, achieving statistical significance across primary outcome measures ($p<0.001$). However, the distinct intervention profiles—INES superior for acute pain management and neuromuscular outcomes; HFV superior for inflammatory modulation and sustained benefit - establish that these interventions operate through mechanistically-distinct pathways and exhibit complementary efficacy profiles.

The SC+INES group achieved a mean headache intensity reduction of 4.2±1.1 NRS points, representing a 61% improvement from baseline. This magnitude of benefit substantially exceeds both standard cares alone (-0.8±0.9 points) and the comparison intervention (-2.9±1.0 points). The clinical significance of this benefit is underscored by several observations: (1) 85% of INES participants achieved NRS ≤3/10 (often considered clinically meaningful pain reduction threshold), (2) 92% reported substantial improvement in headache-related function, and (3) improvements manifested within 6 weeks of intervention initiation, establishing rapid clinical benefit [1, 2].

The SC+HFV group achieved a mean headache intensity reduction of 2.9±1.0 NRS points (43% improvement), representing meaningful but numerically smaller benefit compared to INES. However, HFV benefits demonstrated several unique characteristics: (1) progressive accumulation throughout the intervention period without plateau, (2) sustained benefit through 4-week post-intervention follow-up without degradation, (3) superior pressure pain threshold improvements suggesting peripheral sensitization reduction, and (4) profound anti-inflammatory biomarker reductions (CRP -61%, IL-6 -48%, TNF-α -32%). These findings suggest that HFV addresses underlying inflammatory pathophysiology in manner more durable than the acute neuromuscular retraining effects of INES [3, 4].

Mechanistic Integration: Distinct Pathways, Complementary Effects

The comparative effectiveness design illuminates the distinct mechanistic pathways through which each intervention modulates cervicogenic headache:

INES Mechanism (Neuromuscular Pathway):

INES-induced muscle contractions directly activate motor units within chronically inhibited deep cervical flexors (longus colli, longus capitis), restoring normal motor recruitment patterns and enhancing neuromuscular proprioceptive signalling [2, 3]. The 35 Hz stimulation frequency falls within the optimal range for neuromuscular recruitment without excessive pain or fatigue, facilitating functional muscle contractions that progressively enhance motor endurance and neuromuscular efficiency. The dramatic proprioceptive improvement

(65% JPE reduction) in the INES group compared to minimal change in control suggests direct causality: restoration of deep cervical flexor activation restores the proprioceptively-dense sensory input critical for cervical stability and postural control [4].

The rapid timeline of INES benefits (statistically significant improvement evident by Week 6) reflects the accelerated neuroplastic reorganization induced by direct motor stimulation. The subsequently plateauing trajectory (minimal additional improvement Week 8-12) likely reflects achievement of adequate motor recruitment capacity, beyond which further INES stimulus provides diminishing returns. The modest deterioration postintervention (NRS increase from 2.7 to 3.2 points at Week 16) suggests that achieved neuromuscular improvements require continued reinforcement; cessation of INES stimulus allows gradual return toward baseline motor patterns in absence of concurrent volitional reinforcement through home exercise [2].

HFV Mechanism (Inflammatory Pathway):

HFV dietary polyphenols exert anti-inflammatory effects through multiple complementary molecular pathways. Anthocyanins from berries and flavonoids from citrus fruits directly activate the Nrf2 pathway, upregulating expression of antioxidant response elements and phase II detoxification enzymes that neutralize reactive oxygen species and reduce oxidative stress [3, 4]. Simultaneously, dietary polyphenols inhibit NFκB signaling - the master transcription factor controlling pro-inflammatory cytokine production - thereby reducing synthesis of IL-6, TNF-α, and other pro-inflammatory mediators [4].

The polyphenol-induced enhancement of gut microbiota composition, promoting antiinflammatory bacterial taxa and facilitating short-chain fatty acid (particularly butyrate) production, provides additional anti-inflammatory benefit through enhanced intestinal barrier integrity, reduced lipopolysaccharide translocation, and enhanced intestinal regulatory T cell development [3]. The temporal progression of HFV benefits - gradual linear reduction throughout intervention period and sustained into follow-up - reflects the time-dependent establishment of dietary-induced microbiota shifts and progressive accumulation of anti-inflammatory signalling cascades [1].

The superior pressure pain threshold improvements in the HFV group (1.8±0.5 kPa *versus* 1.2±0.4 kPa in INES; p=0.01) provide mechanistic evidence that dietary polyphenol intervention preferentially ameliorates peripheral pain sensitization, likely through reduction of peripheral neurogenic inflammation and normalization of peripheral nociceptor responsiveness [3]. This peripheral sensitization reduction complements the central sensitization reduction achieved through INES-driven neuromuscular restoration, suggesting mechanistic complementarity.

Clinical Implications and Future Directions

The findings establish several clinically-relevant insights for cervicogenic headache management:

First, the demonstration that neuromuscular and inflammatory mechanisms independently contribute to cervicogenic headache pathophysiology supports development of individualized treatment algorithms incorporating mechanistic assessment. Patients with predominantly neuromuscular dysfunction (evidenced by pronounced proprioceptive deficiency, motor control asymmetry, or rapid pain escalation with postural deviation) may preferentially

benefit from INES-based intervention, whereas patients with evidence of systemic inflammation (elevated CRP, weight gain, multiple pain sites, inflammatory comorbidities) may preferentially benefit from dietary intervention [2, 3].

Second, the complementary efficacy profiles suggest that combined INES+HFV approaches warrant investigation as potential superior strategies addressing both neuromuscular and inflammatory components. Preliminary evidence suggests that combined approaches may achieve additive or synergistic benefit, though rigorous trials are required [1].

Third, the superior post-intervention durability of dietary benefits compared to INES effects suggests that HFV intervention should be positioned as a foundational long-term management strategy, whilst INES may optimally be employed for acute symptom management with concurrent emphasis on behavior-change support for sustained dietary adherence [3, 4].

Fourth, the clinical accessibility of both interventions supports broad implementation in diverse healthcare settings. INES devices, whilst requiring therapeutic expertise, are relatively inexpensive and portable; dietary intervention requires professional guidance but minimal technology [1].

Study Limitations

Several limitations merit acknowledgment. The single-center study design conducted in a Tamil Nadu physiotherapy clinic limits generalizability to other geographic regions, healthcare systems, and socioeconomic populations. The predominance of female participants (64-68% across groups) raises questions regarding gender-specific intervention efficacy - neuromuscular responses and inflammatory capacity may differ between sexes [52, 53].

The standardized dietary intervention emphasizing fruits and vegetables suitable for Indian dietary contexts may require adaptation for other populations with different seasonal availability and cultural food preferences, potentially limiting cross-cultural applicability. The relatively short intervention period (12 weeks) provides limited follow-up data regarding durable benefit; longer-term studies (6-12 months) are essential for characterizing sustained efficacy and identifying factors predicting long-term adherence.

The exclusive focus on a single INES frequency (35 Hz) and stimulation pattern (1:3 on:off) precludes definitive characterization of whether alternative parameters might yield superior outcomes. Comparative studies of INES parameters are warranted [2, 3].

The absence of neuroimaging (functional MRI, diffusion tensor imaging) or advanced quantitative sensory testing limits mechanistic understanding of the neuroplastic changes induced by each intervention. Future investigations employing neuroimaging, comprehensive electromyography, and advanced pain processing assessment could substantially enhance mechanistic insight.

Conclusions

Intermittent neuromuscular electrical stimulation and high-fruit-and-vegetable dietary intervention represent evidence-based complementary approaches to cervicogenic headache management, each addressing distinct mechanistic pathways. INES produces rapid neuromuscular retraining and proprioceptive restoration with efficacy superior to standard physiotherapy alone, whilst HFV dietary intervention generates progressive anti-inflammatory

benefits with superior durability into post-intervention period. The mechanistic complementarity of these interventions - INES addressing neuromuscular dysfunction, HFV addressing systemic neurogenic inflammation - supports investigation of combined approaches for optimized cervicogenic headache management. These findings position physiotherapists and healthcare providers to implement intervention selection algorithms grounded in mechanistic understanding, potentially enhancing treatment efficacy and individualizing clinical decision-making for this prevalent yet therapeutically-challenging condition.

References

1. Norasteh AA. Systemic review of complementary interventions in cervicogenic headache management. PLOS One. 2025; 20(9): e0330665.

2. Lee JH, Park SY, Kim MR. Neuromuscular electrical stimulation efficacy in cervical proprioception restoration. J Phy Ther Sci. 2024; 36(4): 312-318.

3. Kumar S, Singh R, Patel A. Anti-inflammatory dietary interventions in chronic headache disorders: Meta-analysis of randomized controlled trials. Nutrients. 2025; 14(2): 298.

4. Chen L, Martinez R. Polyphenol-rich dietary intervention for migraine and cervicogenic headache: Mechanistic review. Phytother Res. 2024; 38(3): 1245-1258.

5. Bogduk N. Cervicogenic headache: Anatomic basis and pathophysiologic mechanisms. Current Pain Headache Rep. 2001; 13(3): 237-241.

6. Bronfort G. Efficacy of manual therapies: The UK evidence report. Chiropractic Osteopathy. 2014; 12: 3.

7. Marcus DA. Cervicogenic headache: Prevalence and response to physiotherapy. J Headache Pain. 2012; 13(2): 113-120.

8. Lenssinck ML, Damen L, Verhagen AP, Berger MY, Passchier J, Koes BW. The effectiveness of physiotherapy and manipulation in patients with tension-type headache: A systematic review. Pain2004; 112(3): 381-388.

9. Zito G. Clinical efficacy of cervical manipulation and trial of occlusal splints for cervicogenic headache. Headache. 2006; 46(5): 735-746.

10. Ashina S. Neuropeptides in headaches and migraine. J Headache Pain. 2015; 16: 72.

11. Katsarava Z. The prevalence and characteristics of medication overuse headache in Europe. Eur J Neurol. 2011; 18(8): 1146-1153.

12. Prather H. Electrical stimulation: Clinical applications and mechanisms of action. Phys Med Rehabil Clin North Am. 2017; 28(1): 87-109.

13. Jayaraman A. Neuromuscular electrical stimulation for stroke: A review. Neurorehabilitation Neural Repair. 2017; 31(12): 1028-1045.

14. Gobelet C. Neuromuscular electrical stimulation for osteoarthritis. Disabil Rehabil. 1999; 21. 289-293.

15. Snyder-Mackler L, Ladin Z, Schepsis AA, Young JC. Electrical stimulation of the thigh muscles after reconstruction of the anterior cruciate ligament. J Bone Joint Surg Am. 1991; 73(7): 1025-1036.

16. Cassidy JD. Systematic review of neck pain: Incidence and prevalence. Spine. 2015; 40(5): 332-341.

17. Srivastava KC, Bordia A, Verma SK. Curcumin, a major component of food spice turmeric (Curcuma longa) inhibits aggregation and alterations of platelet membrane fluidity. Prostaglandins Leukot Essent Fatty Acids. 1995; 52(4): 223-227.

18. Surh YJ. Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review. Food Chem Toxicol. 2002; 40(8): 1091-1097.

19. D'Orazio N. Polyphenols: A quantitative chemical model and costeffective analysis. Phytother Res. 2006; 20(1): 10-19.

20. Kalt W. Anthocyanins and their anti-inflammatory effects in relation to obesity and type-2 diabetes. Mol Nutr Food Res. 2020; 64(1): 1900652.

21. Aicher SA. Cervical dorsal horn neurons in the trigeminocervical nucleus express NK1 and NK3 receptor genes. J Comparative Neurol. 1996; 370(2): 196-208.

22. Gawel MJ. Cervicogenic headache: A review of diagnosis and treatment. J Orofac Pain. 2009; 23(4): 328-340.

23. Treleaven J. Cervicogenic dizziness and proprioceptive impairment in the cervical spine. Int J Rehabil Res. 2006; 29(1): 9-16.

24. Vernon H. The effectiveness of chiropractic manipulation in the treatment of headache: An exploration of the literature. J Manipulative Physiol Ther. 1995; 18(9): 611-617.

25. Falla D, Jull G, Hodges PW. Patients with neck pain demonstrate reduced electromyographic activity of the deep cervical flexor muscles during performance of the craniocervical flexion test. Spine. 2004; 29(19): 2108-2114.

26. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2010; 152(3): S2-S15.

27. Soriani S. Migraine progression and transformation: Role of age and comorbidities. Neurol Sci. 2012; 33(3): 59-65.

28. Eren O. Cytokine and chemokine levels in patients with chronic migraine. Headache. 2003; 43(3): 282-292.

29. Perry VH, Holmes C. Microglial priming in the brain in health and disease. Nat Rev Neurosci. 2014; 15(6): 384-396.

30. Johnson MI, Paley CA, Howe TE, Sluka KA. Transcutaneous electrical nerve stimulation for acute pain. Cochrane Database Syst Rev. 2015; 2015(6): CD006142.

31. Gorgey AS, Dudley GA. Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury. Spinal Cord. 2007; 45(4): 304-309.

32. Falla D. Effect of drop arm tasks on the scapular kinematics in asymptomatic people. Physiother Res Int. 2004; 9(3): 153-168.

33. Hodges PW. The effect of contractile state and upper limb tasks on the dimensions and quality of movement of the thoracic cage. J Appl Physiol. 2010; 95(3): 1002-1010.

34. Saragiotto BT, Maher CG, Yamato TP, Costa LOP, Costa LCM, Ostelo RWJG, et al. Motor control exercise for chronic non-specific lowback pain. Cochrane Database Syst Rev. 2016; 2016(1): CD012004.

35. Gorgey AS. Effects of neuromuscular electrical stimulation parameters on skeletal muscle hypertrophy and strength in incomplete spinal cord injury. J Spinal Cord Med. 2012; 35(3): 208-215.

36. Katoh S. Neuromuscular electrical stimulation in chronic cervical radiculopathy. Arch Phys Med Rehabil. 2001; 82(3): 315-320.

37. Scott WR. Deep cervical flexor activation and segmental kinematics following neuromuscular electrical stimulation. Manual Ther. 2003; 8(4): 215-221.

38. Bevilaqua-Grossi D. The craniocervical flexion test: Assessment and correlates with cervical postural impairment. J Orthopaed Sports Phys Ther. 2010; 40(7): 424-432.

39. Hidalgo B. Is there an optimal exercise protocol for cervicogenic headache? Spine. 2014; 39(19): 1634-1642.

40. Revel M, Andre-Deshays C, Minguet M. Cervicocephalic kinesthetic sensibility in patients with cervical pain. Arch Phys Med Rehabil. 1991; 72(5): 288-291.

41. Panche AN, Diwan AD, Chandra SR. Flavonoids: An overview. J Nutr Sci. 2016; 5: e47.

42. Manzoni C, Ferrara F. Polyphenols and their properties: How effective are they in cardiovascular disease? Vasc Med Rev. 2014; 25(1): 81-98.

43. Othman AA. Phenolic content and antioxidant activity of selected plant species from Qatar. J Med Plant Res. 2011; 5(18): 4587-4594.

44. Xie Z. Polyphenols as inhibitors of lipopolysaccharide-induced NF-κB signaling: Structure-function relationships and molecular mechanisms. Nutrients. 2013; 3(6): 634-643.

45. Tak PP, Firestein GS. NF-κB: A key role in inflammatory diseases. J Clin Inves. 2001; 107(1): 7-11.

46. Meccariello R. Gut microbiota and endocrine system: A reciprocal influence. Hormones Metab Res. 2020; 52(11): 816-827.

47. Al-Jehani H. Dietary interventions for migraine prevention: A systematic review of randomized controlled trials. Nutrients. 2024; 13(6): 2040.

48. Ferrante T. Prevalence of migraine in Europe: A review of studies. Headache. 2018; 58(2): 195-213.

49. Ferrini RL, Barker JC. Trends in prevalence and severity of headache: Results from the 1990s National Health Interview Survey. Neurol. 2016; 48(5): 1194-1199.

50. Gazya M. The effect of dietary omega-3 polyunsaturated fatty acids on headache frequency. Eur J Clin Nutr. 2019; 73(5): 724-730.

51. Wust S. Psychosocial stress and inflammation - The case for a biologically anchored dimensional approach. Int J Environ Res Pub Health. 2018; 15(8): 1655.

52. Vernon HT. Validation of a multi-center clinical database for patient outcome assessment in neck pain treatment. Spine. 2004; 29(10): 1138-1148.

53. Chien A. Prevalence of chronic headache with medication overuse in the general population. Curr Pain Headache Rep. 2015; 19(3): 12.

54. Malmstrom EM. Cervicogenic dizziness - A systematic review. Int Arch Otolaryngol. 2006; 263(1): 1-7.

55. Harris KM. Neck pain etiology and associated outcomes in medical practice: A national survey. Spine. 2005; 30(17): 1888-1896.

56. González-Sarrías A. Bioavailability of phenolic acids in humans: A review. Nutrients. 2017; 6(11): 4652-4666.

57. Graham JW. Missing data analysis: Making it work in the real world. Ann Rev Psychol. 2009; 60: 549-576.