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Effects of Upper Cervical Spine Manual Therapy on Central Sensitization and Disability in Subjects with Migraine and Neck Pain

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SUMMARY

Background. Migraine is one of the most important causes of disability worldwide and is a frequently accompanied by neck pain. The aim of this study was to evaluate the effect of upper cervical manual therapy (MT) on headache characteristics, central sensitization (CS) and disability in subjects with migraine and neck pain.

Methods. 30 subjects with migraine and neck pain (30 female, mean age 43.10 ± 8.13) were randomly assigned to MT group (MTG), sham MT group (SMTG), and a control group (CG). Central sensitization inventory (CSI) score, disability indices including neck disability index (NDI) and Headache Impact Test (HIT-6), headache characteristics, and medication use were evaluated in all subjects pre and post intervention. Subjects in the MTG and SMTG received either 4 sessions of MT or sham MT. Subjects in the CG received medication only.

Results. Subjects in the MTG had a significant reduction in headache characteristics, medication use, CSI score, and disability indices ($p < 0.05$). CSI score was positively correlated with headache days, headache duration, and NDI score ($p < 0.05$).

Conclusions. Upper cervical MT have beneficial effects on headache symptoms, disability, and CSI score in subjects with migraine and neck pain. The result of this study suggests that MT may be a useful component in the multimodal management of migraine.

Study registration. The trial design was registered in the Iranian Registry of Clinical Trial (IRCT ID: IRCT20160621028567N2, url: https://www.irct.ir/) before the first patient was enrolled.

KEY WORDS

Migraine; neck pain; central sensitization; Neck Disability Index; Headache Impact Test.

INTRODUCTION

Headache is one of the most common, disabling, and recurrent disease (1), with a prevalence estimate of 47% in the global population (2). Migraine is classified as a form of primary headache (3) which affects one in six adults over a 3-month period (4). According to the Global Burden of Disease, migraine is ranked second in the causes of disability (5, 6), which is associated with substantial healthcare resource utilization and costs (7). Migraine is an important reason for absenteeism at work or school (8, 9).

Neck pain is a frequent accompaniment to migraine (10), which can be explained by convergence of trigeminal and

upper cervical neurons in the trigeminocervical complex (TCC) (11). The prevalence of neck pain is reported as much as 80% (10-13) and occurs in all stages of the migraine attack, but particularly during the headache phase (10). The presence of neck pain is associated with more severe headache symptoms (14).

Central sensitization (CS) is a feature of migraine and may be associated with the development of neck pain (12). CS develops through chronic nociceptive input to the central nervous system and, consequently, enhance the function of neurons and nociceptive pathways. Features of CS include widespread and diffuse pain, allodynia and hypersensitivity of the senses. Increased neuronal activity may occur in the brainstem, thalamus as well as somatosensory cortex (15). It has been shown that subjects with migraine were 3 times more likely to have CS (16) and it is assumed that migraine is one of the key components in central sensitivity syndromes. Despite its heavy burden on disability, the treatment of migraine remains inadequate (16). Assessment and consequent appropriate management of CS in migraine may provide a new approach in improving treatment outcomes. The level of CS may also be considered as a marker for treatment responsiveness in subjects receiving treatment for migraine (16).

Many treatments have been proposed for migraine, one of which is manual therapy (MT), possibly due to the high prevalence of neck pain in this condition. MT is an alternative and complementary intervention which has been used in the management of recurrent migraine headaches (17). Articular mobilization techniques of MT refer to low velocity and moderate to high amplitude joint movements (18, 19), which contrast to high velocity manipulation techniques. Mobilization of the upper cervical spine has a positive effect on the inhibitory systems in the spinal cord and can modulate nociception and decrease sensitization (20, 21). Numerous studies show improvement in headache characteristics as well as disability following MT (22-26).

Increasing function and reducing disability associated with migraine attacks are some of the main goals in the management of migraine (27). Disability can be evaluated using questionnaires and are beneficial in research and clinical settings (20, 28). One study revealed the relationship between headache-related disability and healthcare costs (7). Therefore, detailed measurement of disability is important and could be effective in reducing healthcare costs.

A multidisciplinary approach (incorporating MT when neck pain is present) to the management of migraine seems logical particularly in those with high levels of disability and associated CS. However, the effect that MT has on people with migraine and neck pain is poorly understood. The aim of this study was to evaluate the effect of MT on headache characteristics, medication intake, CS, and disability indices in subjects with migraine and neck pain.

MATERIALS AND METHODS

Participants

Thirty participants diagnosed with migraine and neck pain were recruited in this study. Diagnosis was according to ICDH-3 criteria. Subjects with migraine and neck pain were referred from the Headache Clinic, Sina University Hospital, Tehran, Iran. Participants were aged between 18 and 50 years (29) with neck disability index (NDI) score of more than 30% (30, 31). Headache frequency was at least 3 attacks per month and prophylactic medication was unaltered in the previous two months. Subjects with other types of primary or secondary headache, rheumatologic diseases, signs of cervical arterial insufficiency, and instability of the cervical spine were excluded from the study.

The study was conducted in accordance with institutional and international (Declaration of Helsinki) standards. All stages of the study were approved by the Research Ethics Committee at Tarbiat Modares University (approval ID: IR.MODARES.REC.1399.120 – Date of approval: November 09, 2020).

Study design

This randomized controlled trial was carried out at Sina University Hospital. The participants were randomly allocated by sealed envelope method into one of 3 groups: MT group (MTG) (n = 10), sham MT group (SMTG) (n = 10), and control group (CG) (n = 10). Participants in all groups received the same drug regimen and were asked to not change their prophylactic or abortive drugs during the study period. Participants in the MTG received 4 sessions of MT to the upper cervical spine. Subjects in the SMTG received 4 sessions of sham MT to the upper cervical spine. Participants in the CG received medication only. All assessments were taken prior to and ten days following the first intervention session.

Randomization, blinding, and masking

An investigator blind to group allocation performed the assessments and statistical analysis. Randomized allocation was achieved by the sealed opaque envelope method containing group names after primary assessment.

Interventions

All participants were examined for potential contraindications for upper cervical MT (9, 32) including potential

cervical artery defects or cervical spine instability (9, 33). No participant was excluded for this reason. MT and sham MT interventions were performed by an expert physiotherapist with more than 10 years of clinical experience in the use of upper cervical MT.

For the MT intervention, the patients lay supine. The physiotherapist applied 1) central postero-anterior mobilization force, 2) unilateral postero-anterior mobilization force, and 3) unilateral transverse force to each side. All three techniques were non-thrust oscillatory force at 1-2 Hz applied to the vertebral levels of C1, C2, and C3 vertebrae for 30 seconds per level, ensuring to not provoke headache symptoms during the intervention (34, 35).

For the sham MT, the physiotherapist's hand had a broad non-specific contact with the subject's neck and back of the head (36), and no force other than hand contact was applied to the vertebrae.

Both the real and sham MT were applied for the same duration and repeated 6 times within each session. The MT and sham MT interventions were performed on 4 sessions with a one-day interval between each session.

Main outcome measures

A form was given to the participants to record headache characteristics by measuring headache days, headache-free days, headache duration, and headache intensity. The medication intake was recorded through the same form (37).

The six-item Headache Impact Test (HIT-6) was used to assess baseline and monitor change in headache (38, 39). The HIT-6 shows good validity and reliability (38). Neck disability was evaluated using the NDI, which is a valid tool for measuring perceived disability associated with neck pain (40). The NDI is a condition specific disability measure (41) based on the Oswestry disability index (42).

Central Sensitization Inventory (CSI) (43) was used as a proxy for CS and is based on the patient's report. The CSI score was measured using the validated and reliable Persian version of the CSI (44).

Statistics

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, US). The Kolmogorov-Smirnov test was used to determine a normal distribution ($p > 0.050$). Baseline demographic, disability, and headache characteristics of the participants were analyzed using one-way analysis of variance (ANOVA). Between-group change scores were compared using ANOVA and Bonferroni's method as a *post-hoc.* Pearson correlation coefficient was used to extract relationship between variables. Statistical significance was set to $p < 0.05$.

Sample size calculation

To determine the necessary sample size for this study, the mean and standard deviation of headache intensity variable obtained from our previous study (45), was used. The mean of this variable (and standard deviation) before and after intervention was 6.29 (1.30) and 3.85 (1.95), respectively. Using the confidence interval of 95% and test power of 80%, the number of subjects required was 8 in each group. To account for potential dropouts, 10 subjects were included in each group.

RESULTS

Participants

A total of 66 participants were recruited for potential inclusion, with 36 excluded due to not meeting inclusion or not willing to participate in the study. Consequently, 30 subjects (30 female, mean age 43.10 ± 8.13 years) were randomly allocated to MTG, SMTG, and CG (**figure 1**). Baseline demographic, disability, and headache characteristics of the participants are presented in **table I**. There were no significant differences between groups at baseline for any variable.

Headache characteristics and medication use

Participants in the MTG showed a significant reduction in headache intensity, duration, and days ($p < 0.05$) compared to the other 2 groups. Additionally, there was a significant reduction in medication use in the MTG compared to the other 2 groups ($p < 0.05$) (**table II**).

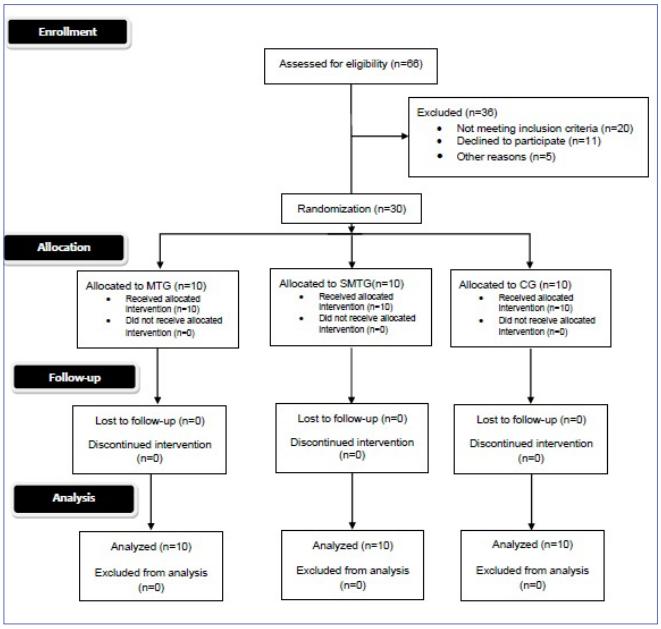

Figure 1. Flow diagram.

Table I. Baseline demographic and headache characteristics.

Variables	MTG (n = 10)	SMTG (n = 10)	CG (n = 10)	P-value
Age (years)	43.10 ± 2.64	43.10 ± 2.64	38.80 ± 3.56	0.509
Gender	10 females	10 females	10 females	-
Weight (Kg)	68.10 ± 3.79	68.10 ± 3.79	70.60 ± 2.93	0.847
Height (m)	1.64 ± 0.02	1.64 ± 0.02	1.68 ± 0.02	0.511
BMI (Kg/m^2)	25.19 ± 1.52	25.19 ± 1.52	24.78 ± 0.52	0.952
Years lived with headache (years)	14.36 ± 2.67	14.36 ± 2.67	13.60 ± 2.17	0.970
Time to peak (hours)	1.45 ± 0.27	1.45 ± 0.27	1.05 ± 0.17	0.422
Headache intensity (VAS 0-10)	8.60 ± 0.33	8.70 ± 0.44	9.10 ± 0.23	0.547
Headache duration (hours)	258.01 ± 26.36	230.10 ± 24.96	269.20 ± 18.66	0.491
Headache days (n)	22.20 ± 2.17	21.50 ± 2.36	24.10 ± 1.95	0.684
Medication intake (n)	21.10 ± 2.11	19.60 ± 2.19	26.50 ± 2.10	0.73
CSI score (%)	52.60 ± 14.75	48.10 ± 15.38	49.00 ± 15.01	0.780
HIT-6	65.90 ± 1.14	67.50 ± 1.31	70.20 ± 1.78	0.121
NDI (%)	58.48 ± 5.44	54.73 ± 5.31	58.20 ± 5.20	0.858

MTG: manual therapy group; SMTG: sham manual therapy group; CG: control group; VAS: visual analogue scale; VAS: visual analogue scale; CSI: central sensitization inventory; HIT-6: Headache Impact Test™; NDI: Neck Disability Index.

Table II. Effect of treatment on headache characteristics and medication use by group.

Variables	Group	Primary assessment	Secondary assessment	Within-group change scores	Between-group change scores		P-value
Headach intensity (VAS 0-10)	MTG	8.60 ± 0.33	4.01 ± 0.36	-4.60 ± 0.45	MTG SMTG	4.50 ± 0.48	< 0.001*
	SMTG	8.70 ± 0.44	8.60 ± 0.33	-0.10 ± 0.27	MTG CG	4.30 ± 0.48	< 0.001*
	CG	9.10 ± 0.23	8.80 ± 0.29	-0.30 ± 0.26	SMTG CG	0.20 ± 0.48	1.000
Headache duration (hours)	MTG	258.01 ± 26.36	124.80 ± 15.15	-133.20 ± 24.72	MTG SMTG	155.10 ± 25.86	< 0.001*
	SMTG	230.10 ± 24.96	252.01 ± 26.54	21.90 ± 11.24	MTG CG	100.90 ± 25.86	0.002*
	CG	269.20 ± 18.66	236.90 ± 13.59	-32.30 ± 16.31	SMTG CG	54.20 ± 25.86	0.137
Headache days (n)	MTG	22.20 ± 2.17	10.10 ± 1.20	-12.10 ± 1.26	MTG SMTG	12.80 ± 1.70	< 0.001*
	SMTG	21.50 ± 2.36	22.20 ± 2.17	0.70 ± 0.84	MTG CG	9.40 ± 1.70	< 0.001*
	CG	24.10 ± 1.95	21.40 ± 1.49	-2.70 ± 1.43	SMTG CG	3.40 ± 1.70	0.170
Medication use (n)	MTG	21.10 ± 2.11	9.40 ± 1.19	-11.70 ± 2.13	MTG CG	13.20 ± 3.37	0.002*
	SMTG	19.60 ± 2.19	21.10 ± 2.11	1.50 ± 1.01	MTG CG	18.10 ± 3.37	< 0.001*
	CG	26.50 ± 2.10	32.90 ± 4.44	6.40 ± 3.39	SMTG CG	4.90 ± 3.37	0.475

MTG: manual therapy group; SMTG: sham manual therapy group; CG: control group; VAS: visual analogue scale; *significant.

Central sensitization inventory scores

Table III shows the intra- and inter-group change scores with 95% confidence intervals in terms of CSI score pre- and post-intervention. CSI scores were significantly reduced in the MTG compared to the other 2 groups ($p < 0.05$).

Disability indices

Disability indices (NDI, HIT-6), in the MTG compared to the other 2 groups were significantly reduced (**table IV**).

Correlations between CSI score and headache characteristics, medication use, and disability

The relationship between CSI score and headache characteristics, medication use, and disability are presented in **table V**. Pearson coefficient revealed a significant positive correlation between CSI score with headache days, headache duration, and NDI score ($p < 0.05$) (**figure 2**).

DISCUSSION

The results of our study showed that upper cervical MT was more effective in reducing headache characteristics, medication use, CSI score, and disability indices than sham MT one month after intervention commenced. It is noteworthy that the CSI score was associated with certain headache characteristics and disability scores. To our knowledge, this is the first study to investigate the effect of upper cervical MT on CSI score in subjects with migraine and neck pain.

Table III. Effect of treatment on central sensitization inventory score by group.

Variables	Group	Primary assessment	Secondary assessment	Within-group change scores	Between-group change scores		P-value
CSI score (%)	MTG	52.60 ± 14.75	43.70 ± 9.27	-8.90 (-13.37, -4.42)	MTG SMTG	11.80 (3.63, 19.97)	0.003*
	SMTG	48.10 ± 15.38	51.00 ± 12.64	2.90 (-3.35, 9.15)	MTG CG	10.01 (1.83, 18.17)	0.013*
	CG	49.00 ± 15.01	50.10 ± 10.96	1.10 (-3.30, 5.50)	SMTG CG	1.80 (-6.37, 9.97)	1.000

MTG: manual therapy group; SMTG: sham manual therapy group; CG: control group; CSI: central sensitization inventory; *significant.

Table IV. Effect of treatment on disability indices by group.

Variables	Group	Primary assessment	Secondary assessment	Within-group change scores	Between-group change scores		P-value
HIT-6	MTG	65.90 ± 1.14	54.10 ± 3.24	-11.80 ± 3.68	MTG SMTG	13.50 ± 3.56	0.002*
	SMTG	67.50 ± 1.31	69.20 ± 1.52	1.70 ± 1.32	MTG CG	11.80 ± 3.56	0.008*
	CG	70.20 ± 1.78	70.20 ± 2.80	0.001 ± 1.94	SMTG CG	1.70 ± 3.56	1.000
NDI (%)	MTG	58.48 ± 5.44	47.74 ± 4.37	-10.74 ± 4.13	MTG SMTG	16.96 ± 4.18	0.001*
	SMTG	54.73 ± 5.31	60.95 ± 5.05	6.22 ± 1.30	MTG CG	18.52 ± 4.18	< 0.001*
	CG	58.20 ± 5.20	65.95 ± 5.25	7.78 ± 2.72	SMTG CG	1.56 ± 4.18	1.000

MTG: manual therapy group; SMTG: sham manual therapy group; CG: control group; HIT-6: Headache Impact TestTM; NDI: Neck Disability Index; *significant.

Table V. Correlations between central sensitization inventory score with headache characteristics, medication use, and disability indicis.

		Headache intensity	Headache days	Headache duration	Medication use	NDI	HIT-6
CS	Pearson correlation	0.201	0.380	0.417	0.248	0.587	-0.077
	Significancy	0.288	0.038*	0.022*	0.187	0.001*	0.688
	n	30	30	30	30	30	30

CS: central sensitization; HIT-6: Headache Impact Test™; NDI: Neck Disability Index; *significant.

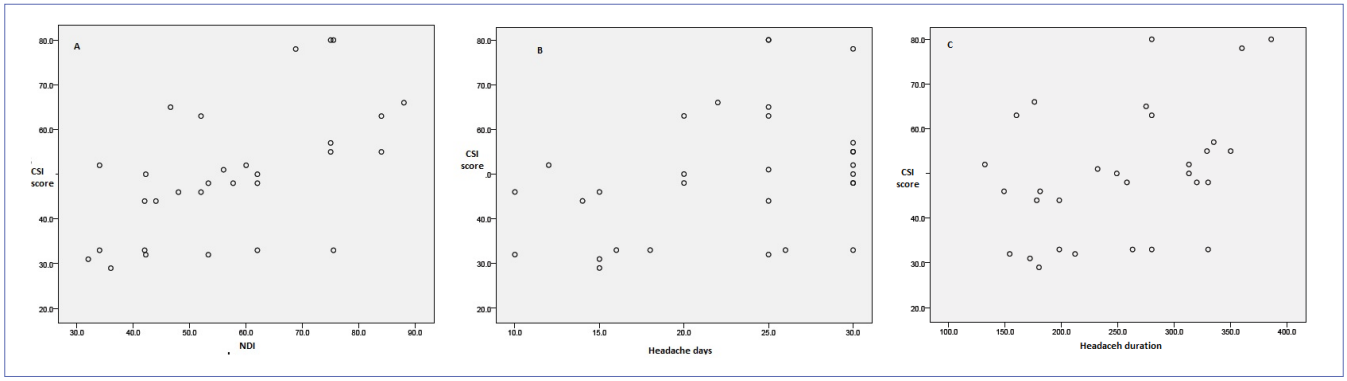

Figure 2. The correlation between SCI score and **(A)** NDI score, **(B)** headache days, **(C)** headache duration showed positive monotonic relationship between central sensitiation inventory score and three other scales.

CS: central sensitization invenory; NDI: neck disability index score.

Evidence supports the non-pharmacological management of headache. A review study reported that MT was similar to tricyclic antidepressants for medium term prophylaxis in subjects with chronic headache (46). Another review study reported that multimodal physiotherapy treatment including MT or relaxation techniques had the same effect as propranolol and topiramate in the prophylactic management of headache (23). It seems, multimodal pharmacological and non-pharmacological treatments together can be more effective in reducing pain, disability and musculoskeletal disorders in migraine.

In our study, the evaluation of a broad spectrum of migraine-related variables including disability indices and CSI score were used to evaluate more details about the effects of MT. Headache characteristics alone may not be enough to reflect migraineur's feeling of improvement (22). Another strength of our study is the use of a sham MT comparator. Real MT led to greater improvement in disability outcomes when compared to both sham MT and a control. Castien *et al.* showed that MT was more effective than usual headache treatment in reducing disability (HIT-6) in the short- and long-term (20). A result consistent with our study. In the present study, the reduction in HIT-6 score in the MTG was significantly greater than in the CG. Another study found that MT combined with exercise had no greater effect in reducing HIT-6 score than usual headache treatments (47). The results of the studies show the possible positive effects of MT in subjects with headache.

The reduction of NDI score in the present study is consistent with that reported by Corum *et al.* (48). Liang *et al.* stated that the NDI may be more reflective of a secondary phenomenon related to migraine pathophysiology and TCC sensitization rather than cervical dysfunction such as physical limitation of neck movement (49). In contrast, some studies suggested that neck pain in subjects with migraine is associated with altered neck mobility, muscle tenderness, and dysfunction (14). Consequently, migraine symptoms may be misinterpreted with perceived neck pain and disability, especially during the migraine attack, which may affect the NDI changes in studies.

Headache improvement in the migraineur patients using upper cervical MT can be explained by pain modulation in the trigeminal nerve territory. This in turn may reduce nociceptive inputs to the TCC through neurophysiological responses specific to the upper cervical segments (48). In other words, upper cervical MT may modulate nociceptive pathways by initiating a cascade of neurophysiological responses from the peripheral nervous system (modulation of inflammatory responses), and the central nervous system at spinal (activation of somato-autonomic reflexes) and supraspinal levels (regulation of brain areas such as anterior cingulate cortex, amygdala or periaqueductal grey) in subjects with migraine (26). There are many mechanoreceptors in the upper cervical region especially in the occipital region, which potentiate mechanical inputs from MT techniques, resulting in decreasing headache symptoms (50).

This study showed a correlation between CSI score with headache characteristics and NDI score. The direct correlation between CSI score with some headache characteristics, and NDI score indicates that more severe headache symptoms are associated with more severe neck disability in subjects with higher CSI scores. These findings provide further evidence for the role of CS in potentiating more severe headache symptoms and disability in migraine sufferers. Fernández-de-las-Peñas *et al.* proposed that MT can play an important role in the management of CS in subjects with headache (1). Nijs *et al.* suggested that MT may target central pain processing mechanisms, and theoretically could desensitize the central nervous system (CNS) (51).

These ideas are supported by the reduction in CSI score in subjects receiving MT in our study, which may be result of neurophysiological effects of MT.
Beside peripheral effects, MT also produces central analgesic effects. However, MT may have short-term analgesic effect, limiting clinical utility in treatment strategies. Potential effects of repeated MT sessions in long-term activation of descending anti-nociceptive pathways should be investigated in future researches (51). However, not much is known about the effects of pharmacological and other treatments on the mechanisms of CS. In conditions characterized by CS, we propose that non-pharmacological treatment with stablished clinical effects can be used along with the pharmacological treatments (51) to achieve better therapeutic effects. Using MT in the clinical management of patients with migraine and neck pain may reduce the excitability of the CNS through neurophysiological inhibitory mechanisms. Further studies are required to examine the detailed role of CS in the management of headache.

Limitations

Several limitations in the present study should be considered. All of the data were collected in the interictal period, which could affect the CSI and disability scores. Another important limitation is the small sample size which could affect the results of study. Furthermore, this study was conducted with one-month follow-up, which was not sufficient to understand long term effects of treatments.

CONCLUSIONS

This study showed that upper cervical MT can improve headache symptoms, disability, and CSI score in subjects with migraine and neck pain. We also found that the level of CSI score and headache symptoms, and NDI score are directly correlated. The result of this study suggests that MT should be considered as part of multimodal management to provide more appropriate treatments for sufferers of this debilitating condition.

FUNDINGS

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DATA AVAILABILITY

All of the relevant data of this study is available in the Dr FB office at Department of Physiotherapy, Faculty of Medical Sciences, Tarbiat Modares University, Jalal AleAhmad, Nasr, Tehran, Iran.

CONTRIBUTIONS

FB, MT: main idea and supervision. FV, MJ: data collection. FB, TH: manuscript revision. MJ: first draft writing.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

REFERENCES

1. Fernández-de-Las-Peñas C, Courtney CA. Clinical reasoning for manual therapy management of tension type and cervicogenic headache. J Man Manip Ther. 2014;22(1):44-50. doi: 10.1179/2042618613Y.0000000050.
2. Racicki S, Gerwin S, Diclaudio S, Reinmann S, Donaldson M. Conservative physical therapy management for the treatment of cervicogenic headache: a systematic review. J Man Manip Ther. 2013;21(2):113-24. doi: 10.1179/2042618612Y.0000000025.
3. Woldeamanuel YW, Cowan RP. Migraine affects 1 in 10 people worldwide featuring recent rise: A systematic review and meta-analysis of community-based studies involving 6 million participants. J Neurol Sci. 2017;372:307-15. doi: 10.1016/j.jns.2016.11.071.
4. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache. 2018;58(4):496-505. doi: 10.1111/head.13281.
5. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain. 2020;21(1):137. doi: 10.1186/s10194-020-01208-0.
6. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22. doi: 10.1016/S0140-6736(20)30925-9.
7. Harris L, L'Italien G, Kumar A, et al. Real-world assessment of the relationship between migraine-related disability and healthcare costs in the United States. Headache. 2022;62(4):473-81. doi: 10.1111/head.14289.
8. Baigi K, Stewart WF. Headache and migraine: a leading cause of absenteeism. Handb Clin Neurol. 2015;131:447-63. doi: 10.1016/B978-0-444-62627-1.00025-1.

9. Muñoz-Gómez E, Inglés M, Serra-Añó P, Espí-López GV. Effectiveness of a manual therapy protocol based on articulatory techniques in migraine patients. A randomized controlled trial. Musculoskelet Sci Pract. 2021;54:102386. doi: 10.1016/j.msksp.2021.102386.
10. Al-Khazali HM, Younis S, Al-Sayegh Z, Ashina S, Ashina M, Schytz HW. Prevalence of neck pain in migraine: A systematic review and meta-analysis. Cephalalgia. 2022;42(7):663-73. doi: 10.1177/03331024211068073.
11. Bogduk N, Govind J. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. Lancet Neurol. 2009;8(10):959-68. doi: 10.1016/S1474-4422(09)70209-1.
12. Carvalho GF, Schwarz A, Szikszay TM, Adamczyk WM, Bevilaqua-Grossi D, Luedtke K. Physical therapy and migraine: musculoskeletal and balance dysfunctions and their relevance for clinical practice. Braz J Phys Ther. 2020;24(4):306-17. doi: 10.1016/j.bjpt.2019.11.001.
13. Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: a population study. Cephalalgia. 2015;35(3):211-9. doi: 10.1177/0333102414535110.
14. Bragatto MM, Bevilaqua-Grossi D, Benatto MT, et al. Is the presence of neck pain associated with more severe clinical presentation in patients with migraine? A cross-sectional study. Cephalalgia. 2019;39(12):1500-8. doi: 10.1177/0333102419854061.
15. Suzuki K, Suzuki S, Haruyama Y, et al. Central sensitization in migraine is related to restless legs syndrome J Neurol. 2021;268(4):1395-401. doi: 10.1007/s00415-020-10295-7.
16. Danno D, Wolf J, Ishizaki K, Kikui S, Hirata K, Takeshima T. Cranial autonomic symptoms in migraine are related to central sensitization: a prospective study of 164 migraine patients at a tertiary headache center. BMC Neurol. 2022;22(1):89. doi: 10.1186/s12883-022-02610-8.
17. Moore CS, Sibbritt DW, Adams J. A critical review of manual therapy use for headache disorders: prevalence, profiles, motivations, communication and self-reported effectiveness. BMC Neurol. 2017;17(1):61. doi: 10.1186/s12883-017-0835-0.
18. Bialosky JE, Beneciuk JM, Bishop MD, et al. Unraveling the Mechanisms of Manual Therapy: Modeling an Approach. J Orthop Sports Phys Ther. 2018;48(1):8-18. doi: 10.2519/jospt.2018.7476.
19. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. Man Ther. 2009;14(5):531-8. doi: 10.1016/j.math.2008.09.001.
20. Castien RF, van der Windt DA, Grooten A, Dekker J. Effectiveness of manual therapy for chronic tension-type headache: a pragmatic, randomised, clinical trial. Cephalalgia. 2011;31(2):133-43. doi: 10.1177/0333102410377362.
21. Watson DH, Drummond PD. Cervical referral of head pain in migraineurs: effects on the nociceptive blink reflex. Headache. 2014;54(6):1035-45. doi: 10.1111/head.12336.
22. Luedtke K, Allers A, Schulte LH, May A. Efficacy of interventions used by physiotherapists for patients with headache and migraine-systematic review and meta-analysis. Cephalalgia. 2016;36(5):474-92. doi: 10.1177/0333102415597889.
23. Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: a systematic review. J Headache Pain. 2011;12(2):127-33. doi: 10.1007/s10194-011-0296-6.
24. Ferragut-Garcías A, Plaza-Manzano G, Rodríguez-Blanco C, et al. Effectiveness of a Treatment Involving Soft Tissue Techniques and/or Neural Mobilization Techniques in the Management of Tension-Type Headache: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(2):211-9.e2. doi: 10.1016/j.apmr.2016.08.466.
25. Varangot-Reille C, Suso-Martí L, Dubuis V, et al. Exercise and Manual Therapy for the Treatment of Primary Headache: An Umbrella and Mapping Review. Phys Ther. 2022;102(3):pzab308. doi: 10.1093/ptj/pzab308.
26. Muñoz-Gómez E, Serra-Añó P, Mollà-Casanova S, et al. Potential Add-On Effects of Manual Therapy Techniques in Migraine Patients: A Randomised Controlled Trial. J Clin Med. 2022;11(16):4686. doi: 10.3390/jcm11164686.
27. American Headache Society. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache. 2019;59(1):1-18. doi: 10.1111/head.13456.
28. Andrasik F, Lipchik GL, McCrory DC, Wittrock DA. Outcome measurement in behavioral headache research: headache parameters and psychosocial outcomes. Headache. 2005;45(5):429-37. doi: 10.1111/j.1526-4610.2005.05094.x.
29. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi: 10.1177/0333102417738202.
30. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther. 1991;14(7):409-15. Available at: https://pubmed.ncbi.nlm.nih.gov/1834753/.
31. Mousavi SJ, Parnianpour M, Montazeri A, et al. Translation and validation study of the Iranian versions of the Neck Disability Index and the Neck Pain and Disability Scale. Spine (Phila Pa 1976). 2007;32(26):E825-31. doi: 10.1097/BRS.0b013e31815ce6dd.
32. Chaibi A, Russell MB. A risk-benefit assessment strategy to exclude cervical artery dissection in spinal manual-therapy: a comprehensive review. Ann Med. 2019;51(2):118-27. doi: 10.1080/07853890.2019.1590627.
33. Côté P, Kreitz BG, Cassidy JD, Thiel H. The validity of the extension-rotation test as a clinical screening procedure before neck manipulation: a secondary analysis. J Manipulative Physiol Ther. 1996;19(3):159-64. Available at: https://pubmed.ncbi.nlm.nih.gov/8728458/.
34. Hengeveld E, Banks K. Maitland's Vertebral Manipulation E-Book: Management of Neuromusculoskeletal Disorders: Elsevier Health Sciences, 2013.
35. Dunning JR, Butts R, Mourad F, et al. Upper cervical and upper thoracic manipulation versus mobilization and exercise in patients with cervicogenic headache: a multi-center randomized clinical trial. BMC Musculoskelet Disord. 2016;17:64. doi: 10.1186/s12891-016-0912-3.
36. Chaibi A, Šaltytė Benth J, Tuchin PJ, Russell MB. Chiropractic spinal manipulative therapy for migraine: a study protocol of a single-blinded placebo-controlled randomised clinical trial. BMJ Open. 2015;5(11):e008095. doi: 10.1136/bmjopen-2015-008095.
37. Jahromi SR, Abolhasani M, Ghorbani Z, et al. Bariatric Surgery Promising in Migraine Control: a Controlled Trial on

Weight Loss and Its Effect on Migraine Headache. Obes Surg. 2018;28(1):87-96. doi: 10.1007/s11695-017-2793-4.
38. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6™) across episodic and chronic migraine. Cephalalgia. 2011;31(3):357-67. doi: 10.1177/0333102410379890.
39. Pryse-Phillips W. Evaluating migraine disability: the headache impact test instrument in context. Can J Neurol Sci. 2002;29 Suppl 2:S11-5. doi: 10.1017/s0317167100001888.
40. Valera-Calero JA, Sánchez-Jorge S, Buffet-García J, Varol U, Fernández-de-Las-Peñas C, Álvarez-González J. Changes in stiffness at active myofascial trigger points of the upper trapezius after dry needling in patients with chronic neck pain: a randomized controlled trial. Acupunct Med. 2022:9645284221104831. doi: 10.1177/09645284221104831.
41. McCarthy MJ, Grevitt MP, Silcocks P, Hobbs G. The reliability of the Vernon and Mior neck disability index, and its validity compared with the short form-36 health survey questionnaire. Eur Spine J. 2007;16(12):2111-7. doi: 10.1007/s00586-007-0503-y.
42. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000;25(22):2940-52; discussion 2952. doi: 10.1097/00007632-200011150-00017.
43. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract. 2012;12(4):276-85. doi: 10.1111/j.1533-2500.2011.00493.x.
44. Noorollahzadeh K, Kahrizi S, Fesharaki MG, Heidarian M, Neblett R, Behzadipour S. Cross-cultural adaptation and psychometric validation of the Persian version of the central sensitization inventory. Musculoskelet Sci Pract. 2021;51:102314. doi: 10.1016/j.msksp.2020.102314.
45. Jafari M, Bahrpeyma F, Togha M. Effect of ischemic compression for cervicogenic headache and elastic behavior of active trigger point in the sternocleidomastoid muscle using ultrasound imaging. J Bodyw Mov Ther. 2017;21(4):933-9. doi: 10.1016/j.jbmt.2017.01.001.
46. Chaibi A, Russell MB. Manual therapies for primary chronic headaches: a systematic review of randomized controlled trials. J Headache Pain. 2014;15(1):67. doi: 10.1186/1129-2377-15-67.
47. De Hertogh W, Vaes P, Devroey D, et al. Preliminary results, methodological considerations and recruitment difficulties of a randomised clinical trial comparing two treatment regimens for patients with headache and neck pain. BMC Musculoskelet Disord. 2009;10:115. doi: 10.1186/1471-2474-10-115.
48. Corum M, Aydin T, Medin Ceylan C, Kesiktas FN. The comparative effects of spinal manipulation, myofascial release and exercise in tension-type headache patients with neck pain: A randomized controlled trial. Complement Ther Clin Pract. 2021;43:101319. doi: 10.1016/j.ctcp.2021.1013199.
49. Liang Z, Thomas L, Jull G, Treleaven J. The Neck Disability Index Reflects Allodynia and Headache Disability but Not Cervical Musculoskeletal Dysfunction in Migraine. Phys Ther. 2022;102(5):pzac027. doi: 10.1093/ptj/pzac027.
50. Rodríguez-Sanz J, Malo-Urriés M, Lucha-López MO, Pérez-Bellmunt A, Carrasco-Uribarren A, Fanlo-Mazas P, et al. Effects of the Manual Therapy Approach of Segments C0-1 and C2-3 in the Flexion-Rotation Test in Patients with Chronic Neck Pain: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(2):753. doi: 10.3390/ijerph18020753.
51. Nijs J, Meeus M, Van Oosterwijck J, et al. Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have? Expert Opin Pharmacother. 2011;12(7):1087-98. doi: 10.1517/14656566.2011.547475.