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ORIGINAL RESEARCH ARTICLE

Effectiveness of manual therapy as a prophylactic treatment for migraine: a randomized controlled trial

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ABSTRACT

Introduction: Migraine is a leading cause of disability worldwide. Although effective, the use of pharmacological prophylaxis is low due to suboptimal efficacy and poor tolerability. This has led to a growing interest in non-pharmacological approaches such as manual therapy (MT), especially among patients with comorbid neck pain. While evidence for MT remains inconclusive, its adjunctive use is recommended. This study evaluated the effect of MT in patients with migraine and neck pain, compared to usual care provided by general practitioners (UC).

Methods: In this randomized controlled trial in primary care, participants with migraine and neck pain were allocated to MT (n = 36) or UC (n = 31). MT included mobilizations, exercises and myofascial techniques. Follow-up assessments were performed at 12-, 26-, and 52-weeks post-inclusion. The primary outcome was the number of migraine days. Secondary outcomes included migraine intensity, disability, medication use, neck pain intensity, neck muscle endurance, pressure pain thresholds, allodynia, and perceived recovery.

Results: There were no significant between-group differences in migraine days or most secondary outcomes. Compared with usual care, the MT group demonstrated significantly higher-pressure pain thresholds over the occipital muscles and reported greater perceived recovery at both 12 and 52 weeks. Use of prophylactic medication was higher in the UC group throughout follow-up.

Conclusion: MT, including postural and cranio-cervical exercises, was not superior to usual care in reducing migraine days and most secondary outcomes. Still, patient preference and treatment satisfaction for MT were high and may be considered in migraine management.

Keywords: Migraine, Manual therapy, Physical therapy, Prophylactic treatment, Randomized controlled trial

What is already known about this topic?

- *Although evidence for manual therapy in migraine remains inconclusive, individuals with migraine frequently use it as a non-pharmacological treatment option.*

What does the study add?

- *Manual therapy, including postural and cranio-cervical exercises, was not superior to usual care in reducing migraine. Patient preference and satisfaction for manual therapy were high, and may provide a patient-centered treatment option in migraine management.*

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Introduction

Migraine is a neurological disorder with a one-year prevalence of approximately 14-15% and is a major cause of ill health worldwide (1). The personal, societal, and economic burden of migraine underscores the need for effective acute and prophylactic treatments (1). In primary care, prophylactic management for frequent migraine (>2 attacks per month) predominantly involves non-specific oral pharmacological therapies such as beta-blockers, anti-epileptic and

anti-depressant medication (2,3). However, data from the OVERCOME (EU) study show that less than 15% of migraine patients with ≥4 migraine days per month use prophylactic medication (4). Concerns about the suboptimal efficacy and poor tolerability commonly lead patients to stop using medication (4). Consequently, over the past decade, there has been a growing interest in non-pharmacological approaches for migraine prevention (5). Manual therapy (MT) represents one such alternative and is increasingly utilized by individuals with migraine (6). This preference for MT may be due to the high prevalence of comorbid neck pain in migraine, affecting up to 75% of patients with migraine (7). A survey among migraine patients who received MT showed that 63% of them reported benefits in migraine frequency, duration and intensity after treatment (6).

Nevertheless, the evidence supporting the effectiveness of MT for migraine is scarce and remains inconclusive, with studies reporting no effect on migraine intensity, duration and quality of life (8), while other studies demonstrate improvements in quality of life and number of migraine days, pain intensity and migraine disability (9,10). Although the overall evidence is limited, MT is recommended as a potential adjunctive therapy in migraine management based on positive findings on quality of life and patient preferences (8).

Migraine is regarded as a neurobiological disorder of the brain, with sensitization of the trigeminocervical complex (TCC) playing a central role in its pathophysiology (11). Coexistent neck pain in migraine is associated with increased pericranial tenderness, suggesting that neck pain (mainly from upper cervical segments C1-C3) may play a facilitatory role in the sensitization process in migraine (12). Not only neck pain but also cervical musculoskeletal dysfunctions, such as myofascial trigger points, reduced neck flexor endurance, and restricted upper cervical mobility, can be present in migraine (13,14). However, whether and to what extent these impairments contribute to, or are a consequence of, migraine remains a subject of debate. Neck pain in migraine does not necessarily reflect musculoskeletal dysfunction, but may be a result of central sensitization of the TCC (15).

Treating painful cervical myofascial structures may reduce peripheral nociceptive input to the TCC (16), and training of cervical muscle function may influence nociceptive transmission (17). Together, these may lead to a decrease in the sensitization of the TCC. Therefore, we postulate that MT targeted at cervical musculoskeletal dysfunction may decrease migraine by decreasing nociceptive transmission within the TCC in patients with migraine and neck pain.

The objective of this randomized controlled trial (RCT) was to assess the effect of a multimodal MT treatment on the number of migraine days and other outcomes in patients with migraine and neck pain, compared to usual care by general practitioners (GPs).

Method

This single-blinded, multicenter, pragmatic clinical trial with two parallel groups evaluated the superiority of multimodal MT treatment over continued usual care by the GP. The study procedures were developed according to the CONSORT and the International Headache Society (IHS) guidelines for randomized clinical trials (18,19). The protocol was approved by the Medical Ethics Committee of VU University Medical Centre, Amsterdam, The Netherlands, and registered in the Dutch medical research portal at Online (registration no. NL-002844). The study protocol has been published previously (20).

Participants

Participants were recruited from April 2019 to January 2023 by 37 GPs in an urban area in the Netherlands. Eligible participants were between 18 and 65 years old, experienced two or more migraine attacks per month, and were diagnosed by a GP or neurologist according to the International Classification of Headache Disorders (ICHD-3) (21). Participants were included if they had concomitant neck pain and were able to understand Dutch.

Exclusion criteria were (suspected) malignancy, pregnancy, cerebrovascular disease, degenerative central nervous system diseases, medication-overuse headache, a current diagnosis of depression or other severe psychiatric disease, rheumatoid arthritis, serious or systemic infection, fever, or change in medication for migraine within three months before the study, and having received MT treatment up to three months before the start of the study. All participants were screened for eligibility by their GP. A researcher performed initial eligibility screening via telephone. At baseline, an independent research assistant reassessed the inclusion criteria, and participants provided written informed consent. Participants with a strong preference for MT who declined randomization were invited to participate in a parallel cohort study. The results of the cohort study will be reported separately.

A four-week run-in period preceded enrollment to establish baseline migraine frequency.

Randomization and blinding

A research assistant blinded to group allocation conducted all baseline and follow-up assessments. An independent statistician generated the random allocation sequence. Participants were randomized using numbered opaque envelopes. A blinded administrative assistant provided the envelope to the participant and arranged the treatment appointment with either the participant's GP or one of the participating manual therapists.

Interventions

Manual therapy (MT) was initiated following assessment of cervical and thoracic function by the manual therapist during the first treatment session. The intervention consisted of a combination of manual pressure techniques applied to the trapezius and suboccipital muscles (22), low-load craniocervical muscle exercises (23), mobilizations of the cervical and thoracic spine (24), and postural correction and exercises (23). The MT intervention had two primary objectives: (i) to reduce cervical nociception by restoring cervical and thoracic musculoskeletal function through mobilization and postural

exercises, and (ii) to enhance central modulation through the use of exercises and manual pressure techniques (25-29). The treatment procedures align with an MT treatment protocol for tension-type headache and were tested in a pilot study (30). High-velocity thrust techniques at spinal levels C0-C3 were not performed due to safety concerns (31). Four experienced manual therapists with over 10 years of experience were trained in the protocol. According to the treatment protocol, manual therapists selected the treatment modalities based on the participant's condition. All participants received posture correction, home exercises, and thoracic mobilization to improve postural alignment and mobility. Cervical mobilization techniques were added when cervical mobility restrictions were identified. Additionally, all participants received manual pressure techniques applied to the trapezius and occipital muscles, aiming to reduce myofascial nociception and enhance central modulation (26). Cervical flexor endurance exercises were prescribed for participants who demonstrated less than 30 seconds on the neck flexor endurance test (32,33).

Home exercise booklets were provided, and participants were encouraged to exercise daily. The intervention consisted of a maximum of nine sessions of 30 minutes. Additional therapies or medication use were discouraged during the treatment period and monitored at each follow-up. Participants were permitted to continue acute or prophylactic pharmacological treatments that had been prescribed prior to study enrollment.

Usual care. Participants allocated to the usual care (UC) group were managed by their GP following the Dutch College of General Practitioners' guideline for headaches (3). All participating GPs received a standardized instruction of the study protocol during a one-hour session led by the research team. Usual care comprised lifestyle advice and, when indicated, the prescription or change of acute or prophylactic pharmacological treatment. Acute treatment options included simple analgesics (e.g., paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs), or triptans. In accordance with the Dutch guideline, prophylactic medication consisted of beta-blockers, anti-epileptics or anti-depressants. After the initial 10-minute consultation, the treatment was evaluated during follow-up consultations at the GPs office or by telephone, at the discretion of the GP.

The treatment duration was 12 weeks for both the intervention and control group.

Outcome assessments

An experienced, blinded research assistant trained in the measurement protocols assessed all outcomes at baseline, 12, 26, and 52 weeks (20).

Primary outcome measures

The primary outcome was the number of migraine days, recorded in a headache diary during the four weeks before each measurement (34).

A clinically important improvement for a migraine patient was defined by a ≥50% reduction in migraine day frequency by comparing the number of migraine days before versus after treatment (34,35).

Secondary outcome measures

Participants recorded the number of migraine attacks in a headache diary. Migraine pain intensity was assessed using an 11-point numerical pain rating scale (NPRS) (0 = no pain, 10 = worst pain). Medication use was recorded as the number of doses per four weeks for simple analgesics, NSAIDs, triptans, and prophylactic medication. Additionally, the frequency of concomitant other headache (classified as tension-type headache according to the ICHD-III criteria (21) was documented in the headache diary over the past four weeks.

Migraine disability was measured using the Headache Impact Test (HIT-6) questionnaire, a validated tool assessing the impact of migraine on pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress (36).

Cutaneous allodynia was evaluated with the 12-item Allodynia Symptom Checklist (ASC-12), categorizing the allodynia severity as none (0-2 score), mild (3-5), moderate (5-8), or severe (≥9) (37).

Pressure pain thresholds (PPTs) were measured to assess local and widespread mechano-sensitivity, using a Wagner FDK algometer at the upper trapezius, suboccipital area, and anterior tibial muscles. Three measurements per site were carried out to reduce variability in measurement (38).

Neck pain intensity was assessed using an 11-point NPRS (0 = no pain, 10 = worst pain).

The endurance of the neck flexor muscles was assessed by the duration (in seconds) participants could raise their head from a supine position, following the method described by Harris et al (32).

Participants reported the global perceived effect (GPE) on a 7-point rating scale (0 = much worse to 6 = much better).

The use of additional healthcare resources and absence from work were documented at each follow-up measurement. Adverse events were recorded at each follow-up for both treatment groups. Detailed information on the measurements and procedures is available in the study protocol (20).

Statistical analysis

A sample size calculation was performed based on data from a pilot study (20). We calculated a sample of 98 participants for each group, considering a minimal reduction of migraine days of at least 25% between groups, a level of significance (α) of 0.05, a power of 80%, and a loss of 15% at follow-up (20). Baseline characteristics between the two groups were compared using descriptive statistics. An intention-to-treat analysis was conducted, using linear mixed-model analyses to analyze the primary outcome and continuous secondary outcome measures across all time points. First, the average intervention effect over time was analyzed by including only the group variable as an independent variable. Next, the intervention effect at the different time-points was analyzed by including the group variable, time (as a categorical variable, represented by dummy variables) and the interaction between the group variable and time. In all analyses, an adjustment was made for the baseline value of the particular outcome variable and a random

intercept on participant level was added to adjust for the correlation between the repeated measures within a participant. For the analysis with pressure pain threshold (PPT), an additional random intercept on PPT location was added to the linear mixed model analysis. The dichotomous outcomes, prophylactic medication use and ≥50% reduction in migraine days were analyzed using logistic Generalized Estimating Equations (GEE) with an exchangeable correlation structure. The results of the GEE analysis will be expressed as odds ratios (OR) and 95% confidence intervals.

In additional analyses, adjustments were made for sex, age, migraine history duration (in years), and presence of concomitant headache. All analyses were performed using SPSS version 29 (IBM Corp., Armonk, NY).

Additionally, a per-protocol analysis was performed for participants who adhered to the study protocol and did not receive additional treatments during the trial (27).

Results

The recruitment of participants in our study was low, primarily due to the challenges posed by the COVID-19 pandemic; as a result, only 67 of the intended 196 participants (10 men and 57 women) were enrolled in the study (Fig. 1). Baseline characteristics are shown in Table 1. During treatment and follow-up, 11 participants (16%) dropped out (6 in the UC group, 5 in the MT group), and four measurements were missing due to COVID-19 restrictions (Fig. 1). No serious adverse events were reported in either group.

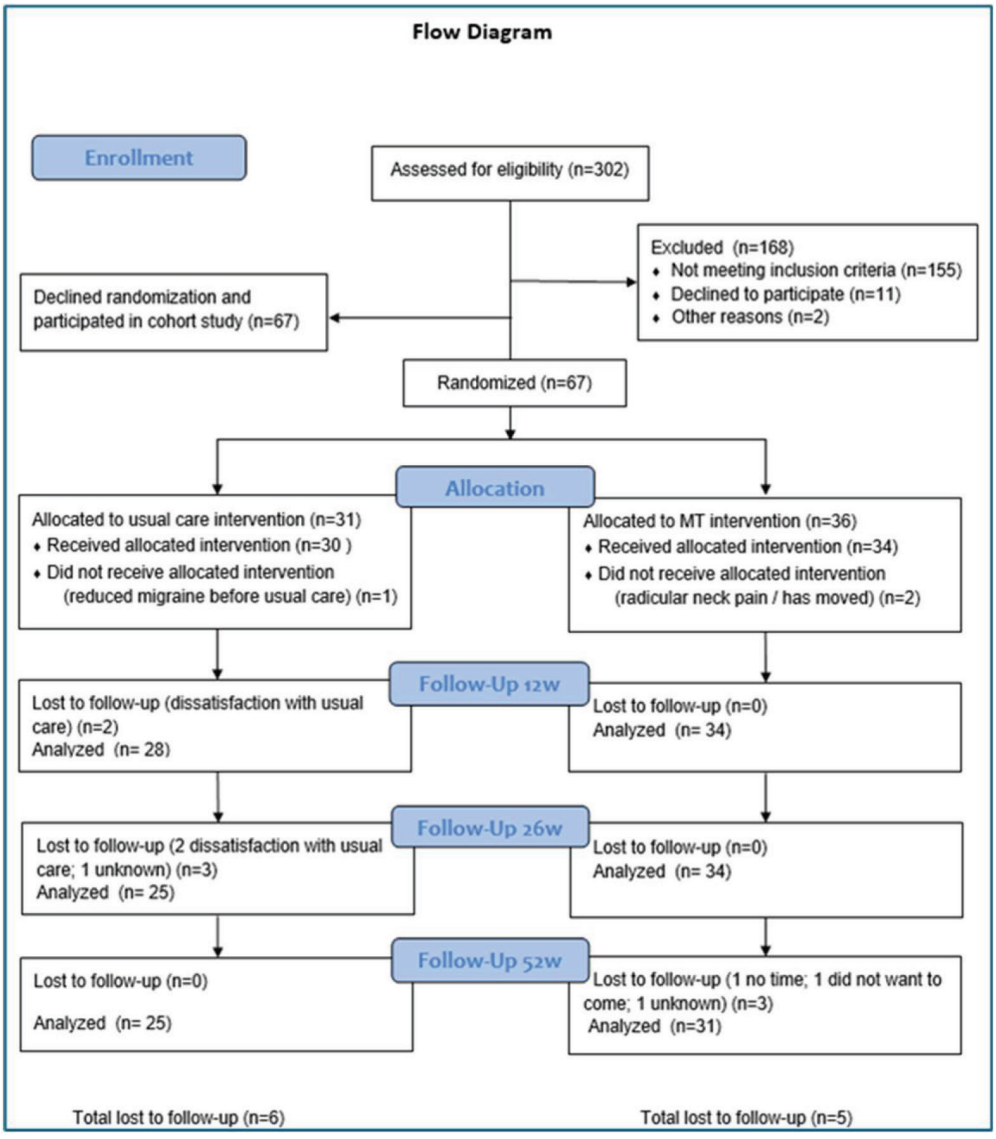

FIGURE 1 - Flowchart according to the CONSORT Statement for the report of randomized controlled trials.

TABLE 1 - Baseline characteristics

	MT group (n = 36)	UC group (n = 31)
Age (mean years)	44.7 (10.1)	44.8 (9.99)
Male/female	5 / 31	5 / 26
Migraine history in years	18.3 (11.7)	19.4 (10.5)
Migraine days/4 weeks	7.28 (4.87)	5.52 (3.01)
Migraine attack	4.28 (2.41)	3.80 (2.59)
Other headache days/4 weeks	5.14 (6.25)	4.71 (4.55)
HIT-6	63.67 (4.90)	64.13 (5.40)
Allodynia score	2.66 (2.23)	3.33 (2.29)
Analgesics use/4 weeks	10.92 (16.34)	6.48 (7.52)
NSAID use/4 weeks	3.00 (6.53)	2.00 (2.97)
Triptan use/4 weeks	3.11 (3.78)	4.90 (7.47)
Prophylactic med. use in %	5.6	6.5
Muscle endurance in seconds	22.66 (16.21)	14.45 (10)
Pressure pain thresholds in kg/cm^2 (average left + right)		
- Occipital muscles	2.59 (1.10)	2.65 (1.19)
- Upper trapezius muscle	3.31 (1.41)	3.24 (1.27)
- Anterior tibial muscle	4.03 (1.64)	4.07 (1.55)

Baseline data in mean values and SD: MT = manual therapy; UC = usual care; n = number; (SD) = standard deviation; HIT-6 = headache impact test; NSAID = non-steroidal anti-inflammatory drugs; kg/cm^2 = kilograms per square centimeter; med. = medication.

Primary outcome (Table 2)

Results of the linear mixed model analyses showed no statistically significant difference in the reduction of number of migraine days between the two groups at 12 weeks follow-up (–1.07; p = 0.22; 95% confidence interval (CI): –2.78-0.65), 26 weeks follow-up (0.61; p = 0.49; 95% CI: –1.13-2.36), at 52 weeks follow-up (–0.66; p = 0.46; 95% CI: –2.43-1.10), and on average over time (–0.38; p = 0 .58; 95% CI: –1.73-0.97). Figure 2 illustrates the number of migraine days in both groups during the trial. The between-group GEE analysis revealed no statistically significant differences in the proportion of participants achieving a ≤50% reduction in migraine days on average (OR: 1.02; 95% CI: 0.44-2.37; p = 0.96). In the MT group, 49% of participants achieved a ≥50% reduction in migraine days at 12 weeks, 44% at 26 weeks, and 39% at 52 weeks of follow-up. In the UC group, a ≤50% reduction was achieved by 38% of the participants at 12 weeks, 46% at 26 weeks, and 29% at 52 weeks (Table 3).

Secondary outcomes (Table 2)

There was no significant difference in group-by-time interaction between the groups in migraine intensity and frequency of migraine attacks averaged over time and at any follow-up moment.

There was no statistically significant difference in the use of analgesics or NSAIDs between the two study groups. The use of triptans showed a significant group-by-time difference at 26 weeks follow-up, with increased use in the MT group (2.23; p = 0.01; 95% CI: 0.58-3.88). In contrast, the use of prophylactic medication differed significantly between the two groups at all time points (Supplementary material Figs 7-10). GEE analysis revealed a higher average use of prophylactic medication in the UC group (OR: 0.09; 95% CI: 0.03-0.30; p < 0.001) and at all time points (Table 3). In the MT group, up to 8% of participants used prophylactic medication throughout the study. In the UC group, prophylactic medication use increased from 6% at baseline to 32% at 12 weeks, 39% at 26 weeks and 29% at 52 weeks.

There was no statistically significant difference in the reduction of migraine-related disability between the groups. Both groups demonstrated within-group improvement, with a greater decrease in HIT-6 scores observed in the MT group (Fig. 3). Other headaches (classified as tension-type headache (28)) decreased significantly in the MT group at the 52-week follow-up with –2.50 headache days (p = 0.03) compared to the UC group (95% CI −4.80 to −0.21).

We found no significant differences in the change in neck pain intensity and neck flexor muscle endurance between the two groups. There was no significant group-by-time effect on allodynia (ASC-12) score between both groups at all time points (Supplementary material Table 4).

The MT group showed a significant increase in PPTs in the occipital region compared to the UC group, both on average over time (0.56; p < 0.01; 95% CI: 0.18-0.94) and at all individual follow-up points. No significant differences between groups were observed in PPT values at the upper trapezius or anterior tibial muscles at any follow-up point (Supplementary material Table 4 and Figs 4-6).

Significantly greater improvement in global perceived effect (GPE) scores was demonstrated in the MT group compared to the UC group when on average over time and at 12- and 52-week follow-ups, but not at 26 weeks (Table 2).

Adverse events in the MT group were short-lasting (1-2 days) and were reported by four participants in the MT group and included nausea (n = 1) and dizziness (n = 1), migraine after treatment (n = 1), and light headache (n = 1). In the UC group, adverse events were reported in five participants and included increased migraine symptoms (n = 1), drowsy/sleepy feeling (n = 3), no appetite (n = 1), and dizziness (n = 1).

Additional analyses

A per-protocol analysis was conducted by excluding two participants who received additional treatments outside the study protocol. The analysis revealed no relevant differences in any of the results compared to the intention-to-treat analysis. Additional intention-to-treat analyses, adjusting for potential confounders (sex, age, duration of migraine history (in years), and the presence of concomitant headache), did not lead to different results regarding the analyses for both the primary and secondary outcomes.

TABLE 2 - Results of mixed model analysis for primary and secondary outcomes

Primary outcome								
		T0	**T1**	**T2**	**T3**	**MT vs UC (T1)**	**MT vs UC (T2)**	**MT vs UC (T3)**
		Baseline	**12 weeks**	**26 weeks**	**52 weeks**	**MD; (95%CI)**	**MD; (95%CI)**	**MD; (95%CI)**
Migraine days	*MT*	*7.28 (4.87)*	*3.69 (2.61)*	*4.71 (4.50)*	*4.31 (3.77)*	–1.07	0.61	–0.66
Mean (SD)	*UC*	*5.52*	*4.31*	*3.83*	*4.62*	(–2.78 to 0.65)	(–1.13 to 2.36)	(–2.43 to 1.10)
		(3.01)	*(2.87)*	*(3.24)*	*(3.57)*	*p 0.22*	*P 0.49*	*P 0.46*
Secondary outcome								
Migraine pain intensity	*MT*	*7.11*	*5.77*	*6.09*	*5.34*	0.32	1.25	–0.52
Mean (SD)		*(1.58)*	*(2.74)*	*(2.71)*	*(2.85)*	(–1.02 to 1.67)	(–0.13 to 2.63)	(–1.92 to 0.87)
	UC	*7.77*	*5.73*	*5.33*	*6.46*	*p 0.64*	*p 0.08*	*p 0.46*
		(1.33)	*(2.81)*	*(2.74)*	*(2.47)*			
Migraine attack freq.	*MT*	*4.28*	*2.71*	*3.23*	*2.53*	–1.03	0.19	–0.91
Mean (SD)		*(2.41)*	*(2.02)*	*(3.28)*	*(1.70)*	(–2.33 to 0.26)	(–1.13 to 1.52)	(–2.24 to 0.43)
	UC	*3.80*	*3.42*	*2.71*	*3.67*	p 0.12	*P 0.77*	*p 0.18*
		(2.59)	*(2.55)*	*(2.91)*	*(3.29)*			
HIT-6	*MT*	*63.67*	*58.34*	*57.94*	*58.34*	–2.54	–2.25	–1.54
Mean (SD)		*(4.90)*	*(8.21)*	*(7.91)*	*(6.53)*	(–6.16 to 1.09)	(–5.96 to 1.45)	(–5.29 to 2.21)
	UC	*64.13*	*60.88*	*60.21*	*60.54*	*p 0.17*	*p 0.23*	*p 0.42*
		(5.40)	*(7.08)*	*(8.83)*	*(6.28)*			
Medication Analgesic use	*MT*	*10.92*	*4.14*	*5.62*	*7.78*	–3.30	–1.37	0.43
Mean (SD)		*(16.64)*	*(4.14)*	*(5.50)*	*(11.28)*	(–6.83 to 0.22)	(–4.99 to 2.24)	(–3.24 to 4.10)
	UC	*6.48*	*6.65*	*6.83*	*6.33*	*p 0.07*	*p 0.46*	*p 0.82*
		(7.52)	*(6.92)*	*(6.67)*	*(7.01)*			
Medication NSAID use	*MT*	*3.0*	*1.49*	*1.88*	*1.66*	–3.35	–2.65	–3.85
Mean (SD)		*(6.53)*	*(2.28)*	*(2.96)*	*(3.10)*	(–7.68 to 0.97)	(–7.00 to 1.69)	(–8.21 to 0.50)
	UC	*2.0*	*2.54*	*4.42*	*5.42*	*p 0.13*	*p 0.23*	*p 0.08*
		(2.96)	*(3.95)*	*(11.28)*	*(16.07)*			
Medication Triptan use	*MT*	*3.11*	*2.77*	*4.26*	*3.16*	–0.55	2.23	1.21
Mean (SD)		*(3.78)*	*(3.90)*	*(5.20)*	*(3.39)*	(–2.16 to 1.06)	(0.58 to 3.88)	(–0.45 to 2.88)
	UC	*4.90*	*3.38*	*2.04*	*2.08*	*p 0.50*	***p 0.01***	*p 0.15*
		(7.47)	*(4.43)*	*(2.56)*	*(2.70)*			
Other headache	*MT*	*5.14*	*2.86*	*2.62*	*2.28*	–1.33	–1.51	–2.50
Mean days		*(6.25)*	*(5.36)*	*(4.82)*	*(4.44)*	(–3.57 to 0.90)	(–3.79 to 0.77)	(–4.80 to
(SD)	*UC*	*4.71*	*3.96*	*3.96*	*4.33*	*p 0.24*	*p 0.19*	–0.21)
		(4.55)	*(3.49)*	*(6.46)*	*(6.15)*			***p 0.03***
GPE n (%) (0-6 cale) #						0.67 (0.12 to 1.21)	0.33 (–0.23 to 0.88)	0.87 (0.31 to 1.43)
- (Very) much improved	*MT*	–	*n = 19(53)*	*n = 15(42)*	*n = 16(44)*	**p 0.02**	p 0.24	***P < 0.01***
	UC	–	*n = 9 (29)*	*n = 10(32)*	*n = 5 (16)*			
- Not improved	*MT*	–	*n = 4 (11)*	*n = 4 (11)*	*n = 4 (11)*			
	UC	–	*n = 12(39)*	*n = 13(43)*	*n = 14(46)*			

Observed mean values (SD) at baseline and follow-up and between-group effects (group-by-time interaction, adjusted for baseline data) for primary and secondary outcomes. MT = manual therapy; UC = usual care; *T0 = baseline; T1 = follow-up at 12 weeks; T2 = follow-up at 26 weeks; T3 = follow-up at 52 weeks;* SD = standard deviation; *MD = mean difference; CI = confidence interval; freq.= frequency; n = number of participants; NSAISs = non-steroidal anti-inflammatory drugs; HIT-6 = headache impact test; GPE = global perceived effect; # Very much improved score 6/6; much improved score 5/6; Not improved score 3/6.*

TABLE 3 -Results of GEE analysis

Dichotomous outcomes								
		T0 Baseline	**T1 12 weeks**	**T2 26 weeks**	**T3 52 weeks**	**MT vs UC (T1) OR; (95%CI)**	**MT vs UC (T2) OR; (95%CI)**	**MT vs UC (T3) OR; (95%CI)**
Migraine days 50% reduction *freq. (%)*	*MT*	–	*n = 17 (49%)*	n = 15 (44%)	n = 14 (39%)	1.20 (0.43 to 3.39) *p 0.73*	0.77 (0.26 to 2.29) *p 0.64*	1.12 (0.34 to 3.60) *p 0.86*
	UC	–	*n = 10 (38%)*	n = 11 (46%)	n = 9 (29%)			
Prophylactic medication *freq. (%)*	*MT*	*n = 2 (6%)*	*n = 1 (3%)*	*n = 2 (6%)*	*n = 3 (8%)*	0.04 (0.00 to 0.38) ***p < 0.01***	0.07 (0.01 to 0.35) ***p < 0.01***	0.21 (0.05 to 0.84) ***p 0.03***
	UC	*n = 2 (6%)*	*n = 10 (32%)*	*n = 12 (39%)*	*n = 9 (29%)*			

Results of GEE analysis for dichotomous outcomes. Observed frequency (%) at baseline and follow-up measurements T0-3, and between-group effects (in OR and 95% CI). MT = manual therapy; UC = usual care; *T0 = baseline; T1 = follow-up at 12 weeks; T2 = follow-up at 26 weeks; T3 = follow-up at 52 weeks;* OR = odds ratio*; CI= confidence interval; freq.= frequency; n = number of participants.*

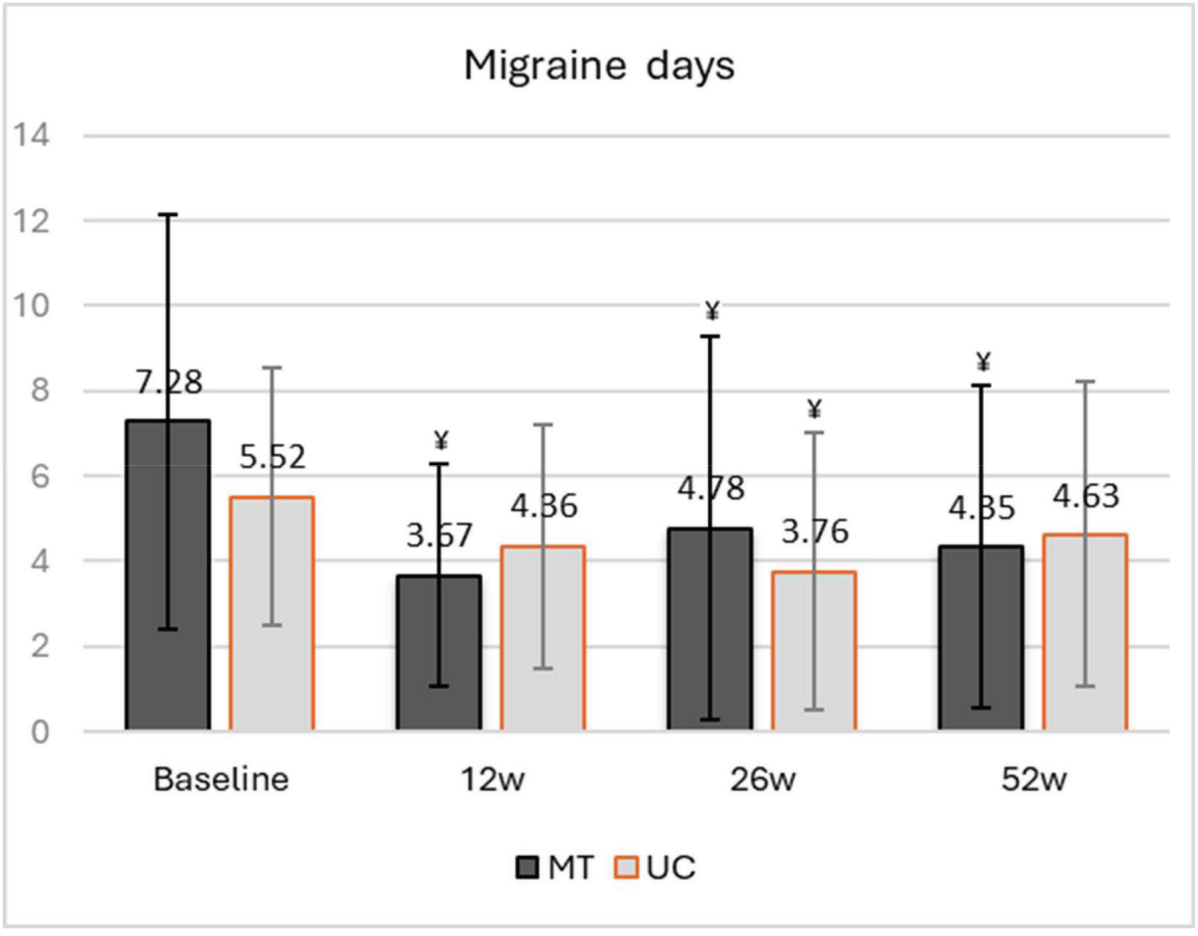

FIGURE 2 - Migraine days; Frequency of migraine days (with standard deviation) per 4 weeks at baseline, 12 weeks, 26 weeks, and 52 weeks follow-up. UC = usual care by the General Practitioner; MT = manual therapy; ¥ = significant within-group difference ($p \leq 0.05$).

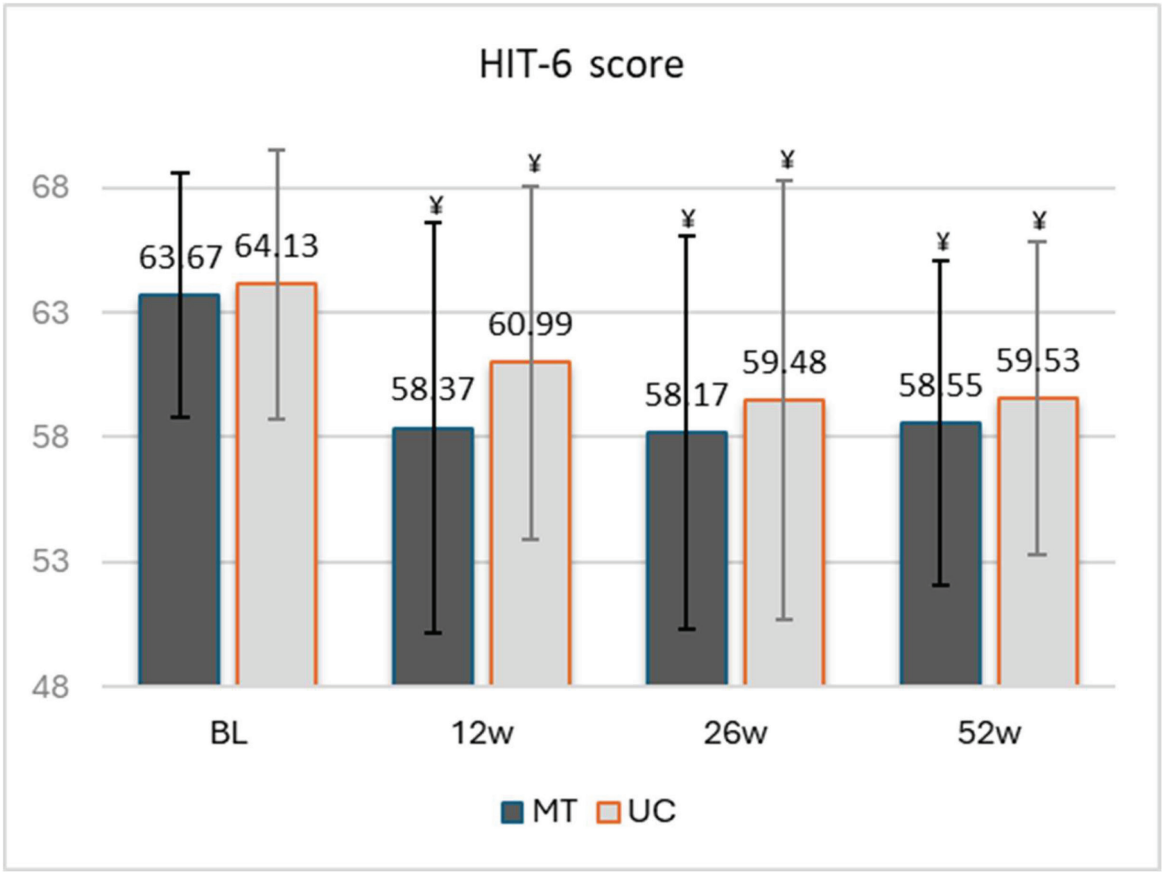

FIGURE 3 - Migraine disability, Migraine-related disability at baseline, 12 weeks, 26 weeks, and 52 weeks follow-up. GP = usual care by the General Practitioner; MT = manual therapy; ¥ = significant within-group difference ($p \leq 0.05$).

Discussion

This study aimed to evaluate the effectiveness of an MT intervention, including postural and cranio-cervical exercises, compared to UC provided by the GP in patients with migraine and neck pain. The results show no difference between MT and UC in the number of migraine days. The absence of significant between-group effects in the number of migraine days is consistent with previous research comparing MT to other active treatments, placebo or standard medical care (39,40). The significant increase in prophylactic medication use (from 6% users at baseline to 39% users during the trial in the UC group, compared to 3% and 8%, respectively, in the MT group) demonstrates the active participation of the GPs and may account for the reduction of migraine days in the UC group. This increase in medication use exceeded our expectations. Previous research evaluating a proactive approach to prescribing prophylactic medication for migraine patients in primary care demonstrated only limited success in increasing medication use and improving care (41). However, 50% of eligible participants declined participation before enrollment in our study due to a negative attitude toward pharmacological treatment. This may have resulted in a preselection of individuals more inclined to accept prophylactic medication. The active management by the GPs in the usual care group was also reflected in the number of consultations during the treatment period (mean 1.75; range 0-6) and in the number of additional medication prescriptions (mean 1.81; range 0-4). In the usual care group, there was an increase in NSAIDs and prophylactic medication use and the prescription of triptans. The strong preference for MT treatment in our study corroborates reports of preference in other trials and observational studies (6,42).

For the secondary outcomes, attack frequency, migraine intensity, migraine disability and allodynia score, no significant differences were found. While Bevilaqua-Grossi et al. (2015) found similar results concerning secondary outcomes, other studies found significant reductions in migraine pain intensity, duration, medication use and migraine disability compared to medication only (43) or placebo (44).

Reductions in headache disability in our study, expressed as HIT-6 scores, exceeded the mean change cutoff for the minimally clinically important change of –2.5 points in both groups (average reduction in HIT-6 score in the MT group −5.46; UC group −3.59) (45).

Significant differences were observed in favour of the MT group for both the perceived effect (GPE) and mechanosensitivity, as measured by pressure pain thresholds (PPTs)

in the occipital region. These findings are consistent with the results of Bevilaqua-Grossi et al., who reported significantly improved perceived recovery and reductions in PPTs in the temporal and trapezius regions, following MT compared to usual medical care, despite finding no between-group differences in the number of migraine days or intensity (39).

We hypothesized that MT may reduce migraine frequency by modulating the transmission of nociceptive afferent input within the trigeminocervical complex (TCC) in patients with migraine and neck pain. Addressing cervical dysfunctions, trigger points and providing cervical exercises aims to reduce peripheral nociceptive afferent input to the TTC. Although the exact mechanisms underlying the modulatory effects of MT remain unclear, several neurophysiological pathways have been proposed to explain these effects. Theoretical frameworks such as the gate control theory (46) and conditioned pain modulation (47) suggest that these interventions may activate inhibitory pathways. These models are supported by hypoalgesic effects observed after exercise in individuals with neck pain, healthy controls, and chronic pain syndromes (17,48). The hypoalgesic effect of spinal manipulation remains a topic of debate, with supposed hypoalgesic effects in some studies (49,50), but conflicting evidence in recent reviews (51). In migraine patients, Jafari et al. demonstrated a reduction in central sensitization and auditory brainstem transmission after MT, indicating a modulatory effect after cervical treatment in migraine patients (52). Additional factors, including environmental influences and patient expectations (53), are also likely to contribute to the therapeutic outcome. Since we did not measure cervical range of motion, we have no information on changes in cervical mobility during treatment.

Although neck pain was not significantly reduced in the MT group, the observed significant decrease in occipital PPTs may reflect a reduction in local sensitization following MT treatment. This reduction in pressure pain sensitivity persisted throughout the follow-up period, up to 52 weeks after treatment, suggesting a long-term modulatory effect of the MT intervention in migraine patients.

Muscle endurance differed significantly at baseline, with higher scores in the MT group. Neck flexor training did not result in a significant increase in muscle endurance compared to the UC group. Our findings are in line with Benatto et al., who reported that neck-specific exercises did not affect the number of migraine days or improve muscle endurance (40). Their study found that neck-specific training was associated with decreased PPTs.

In the UC group, up to 46% of the participants reported no improvement after treatment, compared to 11% in the MT group. The high proportion of participants (53%) in the MT group who reported feeling “much improved” or “very much improved” aligns with the findings of Carvalho et al., who reported a high perceived recovery rate of 63% following MT treatment (7). Perceived recovery following physical therapy interventions is frequently reported, even in the absence of significant between-group differences in migraine days (39,42).

Participants in the MT group who reported comorbid tension-type headache (TTH) experienced a reduction in “other headache“ frequency compared to UC, resulting in a significant between-group difference at 52 weeks follow-up. The effects of MT on TTH may have influenced the perceived recovery at 52 weeks as reported in this study and are in line with research reporting the effectiveness of MT treatment for TTH (54).

The perceived recovery and satisfaction with the MT treatment, as reflected by the GPE score, may be influenced by migraine patients receiving the treatment of their preference. Additionally, the longer time spent with patients during MT sessions may have contributed to the perceived effectiveness of the treatment.

Methodological considerations

Several factors may have influenced the results of our study. Placebo effects in both treatment groups cannot be ruled out. Such effects have been reported in both pharmacological interventions and MT interventions (55). Furthermore, the strong preference for and high expectations regarding MT may have influenced participants’ perceived recovery response in our study (53). Common reasons for the negative attitude towards daily medication use include concerns about potential side effects and previous experiences with ineffective pharmacological treatments (56). Participants in the UC group of our study reported similar reasons for declining pharmacological treatment.

In the UC group, four participants (13%) discontinued treatment because of dissatisfaction with the provided care, which may have influenced the results.

Recruitment for this study was challenging, primarily due to the COVID-19 pandemic. Restrictions on research activities in public health facilities, the need for GPs to prioritize COVID-19-related care, and participants’ hesitancy toward treatment and study procedures all contributed to difficulties in enrollment. Among those who were eligible and approached, 50% declined randomization due to a strong preference for MT treatment, further reducing the number of participants included in the study. As a result, the predefined sample size of 96 participants per group was not achieved.

Strengths and limitations of the study

A key strength of this study is its pragmatic design, reflecting routine clinical practice in primary care, the long-term follow-up of 52 weeks, and the adherence to the CONSORT and the clinical trial guidelines of the IHS concerning the inclusion, outcome measures and statistical analysis (18,19).

However, this study has several limitations. First, we recruited fewer patients than our power analysis requested, 67 instead of 196 participants, limiting the statistical power to detect potentially meaningful effects and reducing the generalizability of the results. Secondly, this trial was conducted during the COVID-19 pandemic, a period during which participants’ daily activities were significantly disrupted. These disruptions may have influenced the reporting of migraine symptoms. Thirdly, manual therapists and GPs were not blinded to group allocation due to the nature of the intervention. The lack of blinding may have introduced performance bias. Finally, participants’ preference for MT may have

influenced their perception of treatment efficacy, particularly among those assigned to the UC group, potentially contributing to differential dropout or response bias (53).

Recommendations

The results of this study contribute to the growing body of evidence on non-pharmacological prophylactic treatment options for individuals with migraine. However, due to the current lack of high-quality evidence regarding the efficacy of MT for migraine prophylaxis, further rigorous and adequately powered randomized controlled trials are warranted. Future studies should include assessments of cervical mobility to determine whether cervical mobility is associated with changes in migraine characteristics and to identify subgroups of patients who may be more likely to benefit from MT (57). Our findings suggest that patients receiving physiotherapy may also value outcomes other than migraine frequency or a ≥50% reduction rate, such as quality of life and global perceived effect. Consideration of additional patient-centered outcomes may therefore be relevant in clinical practice and future research (58).

The results of such studies should enhance clinical decision-making by guiding GPs and patients seeking non-pharmacological treatment options for migraine in primary care.

The results of the present study suggest that, in addition to prophylactic medication, MT may serve as an adjuvant prophylactic treatment option for patients with frequent migraines and neck pain, particularly for those who experience side effects of medication or hold a negative attitude towards daily medication use. The high level of participant satisfaction following MT in our study may account for the potential value of MT as an adjunctive prophylactic treatment option and may support a patient-centred approach in primary care. However, more research is needed to draw conclusions on the effectiveness of MT for migraine.

Conclusion

Compared to usual GP care, MT, in combination with postural and cranio-cervical exercises, was not superior in reducing migraine days and most secondary outcomes. Still, patient preference and treatment satisfaction for MT were high and may be considered in migraine management.

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Conflict of interest: The authors declare to have no competing interests.

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Consent for publication: All participants provided written informed consent before inclusion in the study

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