International Journal of Osteopathic Medicine 43 (2022) 5–15

Contents lists available at ScienceDirect

International Journal of Osteopathic Medicine

journal homepage: www.elsevier.com/locate/ijosm

Short- and medium-term effects of manual therapy on the upper cervical spine combined with exercise vs isolated exercise in patients with cervicogenic headache. A randomized controlled trial

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ARTICLE INFO

Keywords:
Cervicogenic headache
Exercise
Manual therapy
Upper cervical spine

ABSTRACT

Background: Cervicogenic headache is defined as a unilateral headache associated with a lack of range of motion. The effect of manual therapy applied to the upper cervical spine combined with cervical exercises in this patient population is currently unknown.
Objective: To determine if adding manual therapy to an exercise and home-exercise program is more effective by reducing symptoms and improving function in the short- and mid-term than just applying exercises in patients with cervicogenic headache.
Methods: Randomized controlled trial. 40 participants with cervicogenic headache were recruited (20 = Manual Therapy + Exercise and 20 = Exercise). Each group received four 20-min sessions weekly and a home exercise regime. Upper cervical flexion and flexion-rotation test, HIT-6, headache intensity, craniocervical flexion test, pain pressure thresholds, GROC-scale, and adherence to self-treatment were measured at the beginning and end of the intervention, and again at 3-(short-term) and 6-month (mid-term) follow-ups.
Results: The Manual Therapy + Exercise group showed a statistically significant improvement in all short- and mid-term variables ($p < .05$) compared to the exercise group except for the variable pain pressure thresholds first metacarpal joint right and left short-term and adherence to self-treatment short-term.
Conclusion: Four 20-min sessions of manual therapy and an exercise protocol along with a home exercise regime is more effective in the short and mid-term than an exercise protocol and a home exercise regime for patients with cervicogenic headache.

1. Introduction

Cervicogenic headache is a secondary headache defined as a unilateral headache associated with neck pain. The prevalence of cervicogenic headache has been reported to be between 0.4 and 20% of the headache population [1,2]. Symptoms include a lack of cervical range of motion, pain upon palpation of different neck structures, especially the upper cervical spine [3,4], weakness of the deep flexor muscles [5], and disability caused by the headache [6,7].

The flexion-rotation test and the craniocervical flexion test are two validated tests that partially assess the upper cervical spine. The flexion-rotation test is used to measure upper cervical rotation. This test is

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https://doi.org/10.1016/j.ijosm.2022.04.006
Received 6 April 2021; Received in revised form 4 March 2022; Accepted 1 April 2022
Available online 5 April 2022

considered positive for an upper cervical spine restriction if there is an asymmetry >10° between sides or a cervical rotation less than 32° in any direction [8]. The craniocervical flexion test measures the activation of the deep flexor muscles. The craniocervical flexion tests requires a large range of cervical flexion in order to be performed [9].

Restoration of the upper cervical spine mobility is considered one of the main objectives for the treatment of cervicogenic headache [4]. Manual therapy interventions seek to restore upper cervical mobility through a wide range of therapeutic procedures, including mobilization and manipulation techniques [4,10]. Several systematic reviews report evidence supporting the application of upper cervical spine manual therapy techniques for the management of cervicogenic headache [11, 12].

Cervical exercises have been shown to be effective and safe for the treatment of different cervical conditions, including cervicogenic headache [13], in isolation [5] or combined with manual therapy [13, 14]. However, these studies do not have inclusion criteria of upper cervical spine restriction and deep cervical flexor muscle weakness. A recent study supported adding manual therapy to a cervical training in patients with chronic neck pain and upper cervical spine restriction measured with the flexion-rotation test [15]. This study found significant improvements in functional and symptomatic variables when manual techniques were applied in upper cervical spine to restore motion before performing cervical training [15]. However, this association has not been studied in cervicogenic headache patients.

The objective of this study was to determine if adding manual therapy to an exercise and home-exercise program is more effective by reducing symptoms and improving function in the short- and mid-term than just applying exercises in patients with cervicogenic headache.

2. Methods

2.1. Study design

A randomized, parallel (simple 1:1) controlled trial was conducted. An outside researcher performed the randomization using Microsoft Excel 2010 for Mac. Assignments were placed in a concealed opaque envelope, and participants were randomly assigned to intervention groups.

The study was designed in facilities at the University of Zaragoza (Clinicaltrials.gov number: NCT04401501). This study complied with the ethical principles for medical research on human participants and was approved by the local ethics committee (13/2018).

2.2. Sample size calculation

The sample size was calculated based on the outcomes of Malo-Urriés et al. (2017) [4]. The common standard deviation and the minimum differences to be detected between the groups were also determined using the outcomes of the Malo-Urriés et al. study [4]. The main variable used for sample size calculation in our study was the flexion-rotation test [4], thereby requiring 20 participants per group, for a total of 40 participants. The sample size was calculated using GRANMO 7.12, with a α risk of 0.05, test two-side, a β risk of 0.20. For the flexion-rotation test variable, we used an estimated common standard deviation of 7.58 [4] and a minimum expected difference of 7.37 [4], estimating a follow-up loss of 15%.

2.3. Participants

Forty participants (12 men, 28 women) were recruited from 86 individuals with cervicogenic headache. Diagnosis of cervicogenic headache, according to Sjaastad et al. [16] was used as the inclusion criteria. Participants had to fulfill both parts I and III of the primary criteria for diagnosis (pain aggravated by neck movement, sustained position or external pressure, restricted cervical range of motion, and unilateral pain starting in the neck and radiating to the frontotemporal region) [16]. Additional inclusion criteria included: hypomobility in one or more segments of C0-1, C1-2, C2-3 through manual evaluation [17,18] with a reliability between 0.78 and 1 and an excellent validity [19] in cervical disorders [17,20], a positive result in the flexion-rotation test [21–23], a failure to pass stage 2 (24 mmHg) of the craniocervical flexion test [23,24], age 18 years or older, and a signed informed consent. Exclusion criteria included: contraindications for manual therapy or exercise, participation in exercise or manual therapy programs in the last three months, inability to maintain supine position, the use of pacemakers, inability to perform flexion-rotation test, inability to read or understand the informed consent, and pending litigation or lawsuits [25].

3. Measurements

The primary outcome measures included in this study were the Impact Headache Test-6 questionnaire (HIT-6) and flexion-rotation test. The secondary outcome measures were active flexion of the upper cervical spine, headache intensity, craniocervical flexion test, pressure pain threshold (PPT), global rating of change scale (GROC-Scale) and adherence to self-treatment scale. Active flexion of the upper cervical spine was measured in a standing position using a CROM device [26]. Upper cervical rotation was measured with a CROM using the flexion-rotation test, per Hall et al. (2007) [21]. Three measures were taken for each test and averaged for the purposes of this study.

The craniocervical flexion test was used to measure the activation of the deep flexor muscles. The activation and resistance of the deep flexor muscles was evaluated in five progressive pressure increases of 2 mmHg up to a maximum of 30 mmHg. The patient passed to the next level after reaching a given level three times [27].

Headache intensity was assessed on a visual analog scale (VAS) from 0 to 10 cm, with no intermediate point. The VAS has demonstrated excellent reliability (ICC 0.92) [4,28].

The HIT-6 (reliability >0.70) was used to describe the degree of pain and disability caused by the headache [6,7,29–31]. The results are classified into four categories that score daily life impact of headache (little or none, some, substantial and severe) [32].

The PPT was measured using a digital algometer (Somedic AB Farsta, Somedic SenseLab AB, Sweden) with a round surface area of 1 cm^2. Pressure was applied at a rate of 1 $kg/cm^2/s$, perpendicular to the skin. The PPT was assessed over six points bilaterally with the participant in supine: suboccipital region, C2-3, C5-6, levator scapulae, trapezius and first metacarpal joint. Participants were instructed to press the button of the algometer at the point pressure changed to pain. The mean of three trials was calculated over each point and used for analysis. PPT reliability has shown to be excellent (ICC = 0.92–0.99) [4,33,34].

The GROC-Scale (ICC = 0.90) was used to measure the participant's perception of positive or negative changes associated with the intervention [35–38].

A novel scale was used to measure participant adherence to self-treatment at home. Patients were asked to choose between the following answers: "I have done the exercises every day"; "I have performed the exercises 4–6 days a week"; "I have performed the exercises 1–3 days a week"; "I have performed the exercises less than 1 day a week"; or "I have not performed them". The researcher (A) contacted patients individually via video conference every ten days to make corrections according to their self-treatment program.

Another researcher (B) with training in evaluation and more than six years' clinical experience, carried out the measurements before (T0), at the end of the intervention (T1), after three months (short-term) (T2) and after six months (mid-term) (T3). Researcher B remained blinded to patient group assignment throughout the process. Study participation was then complete, and researchers proceeded with an individualized treatment approach.

3.1. Intervention

Treatment was applied by researcher A, a therapist with more than six years' experience in manual therapy. The intervention was administered individually in the facilities of the University of Zaragoza. Participants in both groups received one 20-min session, once a week for four weeks, and home exercises every day between two and five times a day, starting after the first session [14,39–41]. A weekly video call was made to monitor their home exercise adherence.

3.2. Exercise Group

The participants were instructed in an exercise program one day a week for four weeks. Each exercise session lasted 20 min and was composed of two blocks of 10 repetitions, holding each exercise for 10 s, with a 40-s rest between each repetition, and 2 min between blocks [42].

The exercise program was developed according to Fernández-de-las-Peñas et al. (2013) [42] and Jull et al. (2002) [14]. This exercise progression includes the contraction of deep neck flexor muscles (Fig. 1) in the first session. In the second session, the deep neck extensors were performed in a quadruped position. They started with the head bent down onto their chest and progressed with a segmental extension movement [42]. In the third and fourth sessions, the patient trained craniocervical flexion in supine by lifting the head off the table while keeping the spine in a neutral position [42]. The patient also activated the extensors against an external resistance in a quadruped position [42]. If a patient was not able to do an exercise, it was adapted so that they could perform it successfully.

Manual Therapy + Exercise Group (MT + E).

The MT + E program was conducted once a week for four weeks. Each session lasted 20 min. Manipulation (high velocity, low amplitude) (Fig. 2) and/or mobilization (low velocity, high amplitude) of the upper cervical spine, including the C2-3 segment [4,17,18,43,44], combined with cervical exercise, were performed. The manual therapy techniques used depended on each patient's clinical findings. The goal of the manual therapy intervention was to restore upper cervical spine function before applying cervical exercises. Training exercises performed by this group followed the same progression and amounts as the exercise group [14,42].

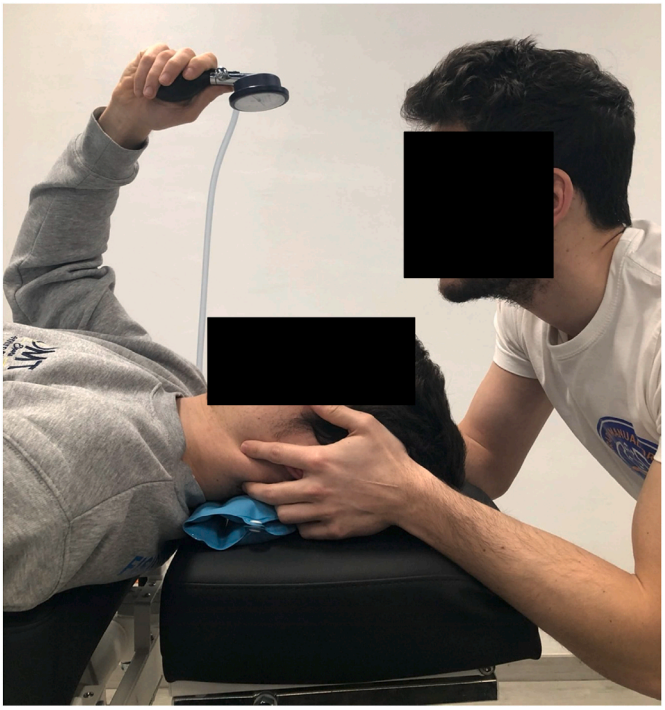

Fig. 1. An Example of Contraction of deep neck flexor muscles.

Fig. 2. An example of traction-manipulation in the resting position C2-3.

All manipulation and mobilization techniques were performed with translational movements with the cervical spine near mid-position. All techniques followed IFOMPT recommendations to reduce the risk of adverse effects, so that treatment of segment C0-1 and C2-3 was prioritized over that of segment C1-2. This criterion prioritizes treatment of the segments with the lowest risk and addresses only if necessary, treatment of the segment with the highest risk (C1-2) last [45]. Manipulations were applied in the direction of traction, with the head in a neutral position [46]. A maximum of two trials at each level was performed on each side, yielding 2–6 thrusts at each visit [47]. Mobilization was performed for 5 min using repeated cycles of 45 s of mobilization and 15 s of rest [4,44].

3.3. Statistical analysis

Statistical analysis was performed using SPSS 25.0 package (IBM, Armonk, New York). The mean and standard deviations were calculated for each variable. The Kolmogorov–Smirnov test was used to determine a normal distribution of quantitative data ($p > .05$). Within- and between-group differences were analyzed using repeated measures ANOVA and one-way ANOVA for quantitative variables. For qualitative variables, Fisher's exact test was used. Effect sizes were calculated using Cohen's d coefficient [48]. An effect size >0.8 was considered large; around 0.5, intermediate; and <0.2, small [48]. All initial participating subjects were included in the final analysis on an intention-to-treat basis (Little's missing completely at random test and expectation maximization). The level of significance was set at $p < .05$.

4. Results

Eighty-six volunteers were recruited from June 2020 to January 2021. Forty participants (12 men, 28 women) with a mean age of 49 (SD:13.7) met all eligibility criteria and agreed to participate. Twenty

were randomly assigned to the exercise group and 20 to the MT + E group. Participants received their assigned treatment and were analyzed for intention-to-treat. Drop-outs, enrollment, exclusions after randomization and follow-ups are provided in the flow diagram, see Fig. 3. The sample demographics are summarized in Table 1.

No moderate or severe adverse events were reported following any manual therapy treatments applied during the study. However, four exercise group participants reported treatment side-effects such as mild and transient aggravation of headache in the end of the intervention (3 participants) and after 3-month follow-up (1 participant). In the MT + E group there was one participant with transient aggravation of headache in the end of the intervention.

4.1. End of the intervention (T1)

In the within-group analysis of the exercise group, a statistically significant increase in the craniocervical flexion test was found ($p < .002$) (Fig. 4). In the MT + E group statistically significant improvement in the headache intensity ($p < .006$), HIT-6 ($p < .001$), right and left flexion-rotation test ($p < .001$) and craniocervical flexion test ($p < .001$) was found (Table 2; Fig. 4).

In the between-group analysis (Table 3), statistically significant differences were found between both groups in favor of the MT + E group in the headache intensity ($p < .001$), right and left flexion-rotation test ($p < .001$) and in PPT variables of the levator scapulae muscles right) ($p < .015$), C2-3 (right) ($p < .043$), suboccipital (right) ($p < .040$) and C5-6 (left) ($p < .031$). Differences in the GROC-Scale were also found ($p < .003$) (Fig. 5).

In terms of self-treatment, 57.9% (MT + E) and 66.7% (Exercise) accomplished self-treatment every day, 31.6% (MT + E) and 19% (Exercise) between 4 and 6 days a week and 10.5% (MT + E) and 14.3% (Exercise) between 1 and 3 days a week. There were no significant differences between groups ($p > .648$).

4.2. 3-Month follow-up (T2)

In the within-group analysis (Table 2) of the exercise group, a statistically significant decrease in the suboccipital (right) ($p < .048$) and levator scapulae (left) PPT ($p < .044$) was found. A statistically significant increase in the craniocervical flexion test was also found ($p < .001$) (Fig. 4). In the MT + E group, a statistically significant improvement was observed in the headache intensity ($p < .001$), upper cervical spine flexion ($p < .010$), HIT-6 ($p < .001$), right and left flexion-rotation test ($p < .001$) variables. There was a statistically significant increase in the PPT variables at C5-6 (right) ($p < .05$), suboccipital (right) ($p < .006$), C5-6 (left) ($p < .015$), C2-3 (left) ($p < .026$) and suboccipital (left) ($p < .002$). There was also a statistically significant increase in the craniocervical flexion test ($p < .001$) (Fig. 4).

In the between-group analysis (Table 3), statistically significant differences were found between both groups in favor of the MT + E group in the headache intensity, upper cervical spine flexion right and left flexion-rotation test ($p < .001$) variables, HIT-6 ($p < .009$) and in the PPT variables of trapezius (right) ($p < .024$), levator scapulae (right) ($p < .004$), C5-6 (right) ($p < .002$), C2-3 (right) ($p < .003$), suboccipital (right) ($p < .001$), trapezius (left) ($p < .014$), levator scapulae (left) ($p < .001$), C5-6 (left) ($p < .001$), C2-3 (left) ($p < .004$) and suboccipital (left)

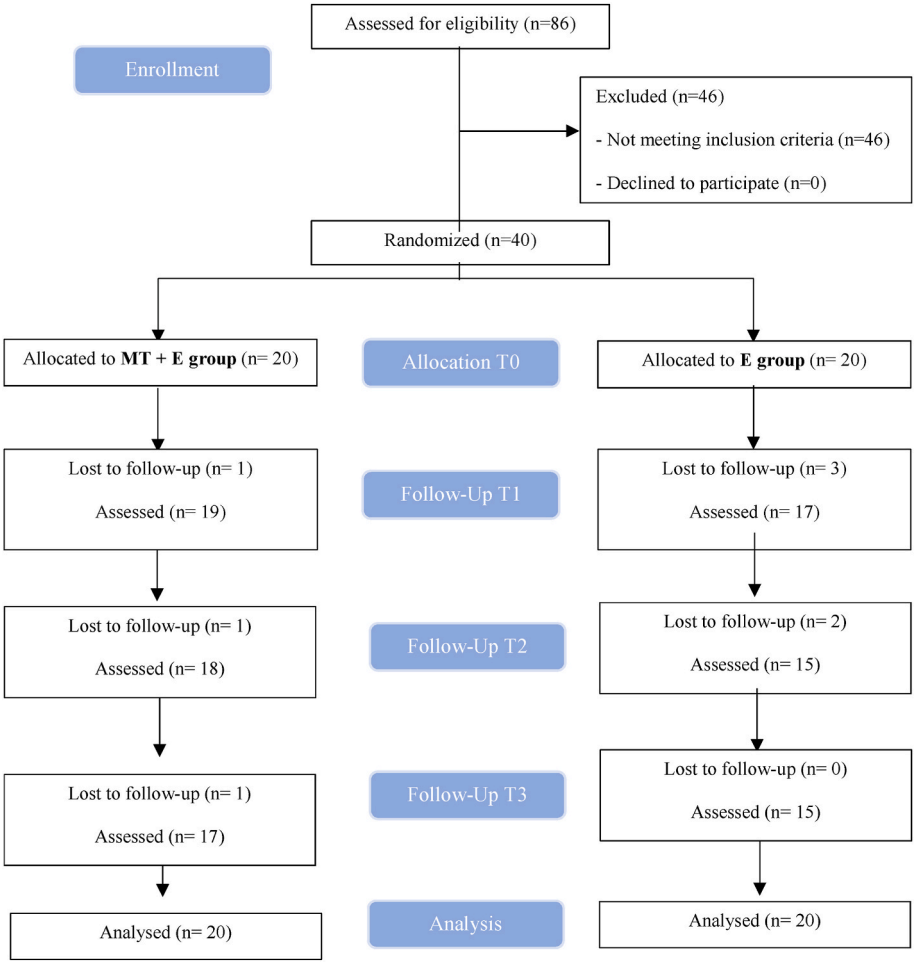

Fig. 3. CONSORT. (Consolidated Standards of Reporting Trial) flow diagram.

Table 1
Baseline features for both groups.

	MT + E Group (n = 20)	Exercise Group (n = 20)
Clinical features		
Age (years)	49.05 ± 13.70	47.90 ± 19.56
Sex	31.6% M	28.6% M
	68.4% F	71.4% F
Daily	31.6%	19%
Weekly	36.8%	42.9%
Monthly	31.6%	33.3%
Quarterly	0%	4.8%
Headache Intensity (cm)	3.41 ± 1.94	3.63 ± 2.28
Upper Cervical Flexion (°)	10.84 ± 4.45	10.52 ± 4.50
HIT-6	57.22 ± 8.83	56.33 ± 7.64
Craniocervical flexion test		
Doesn't get it	26.3%	33.3%
20 mmHg	21.1%	33.3%
22 mmHg	52.6%	33.3%
Flexion-rotation test (°)		
Right	20.61 ± 11.17	17.68 ± 10.24
Left	22.89 ± 8.17	19.78 ± 10.62
Pressure Pain Threshold (Kpa)		
FMJ (R)	398.37 ± 221.50	389.57 ± 193.87
Trapezius (R)	213.90 ± 111.73	207.43 ± 98.24
Levator scapulae (R)	218.89 ± 159.48	195.24 ± 118.47
C5-6 (R)	174.84 ± 95.23	158.71 ± 71.04
C2-3 (R)	208.37 ± 132.09	187.19 ± 99.41
Suboccipital (R)	216.89 ± 107.87	193.14 ± 82.81
FMJ (L)	356.16 ± 214.81	381.76 ± 176.15
Trapezius (L)	245.00 ± 132.36	234.76 ± 103.30
Levator scapulae (L)	230.58 ± 165.80	213.14 ± 134.94
C5-6 (L)	178.32 ± 87.77	165.81 ± 80.62
C2-3 (L)	211.00 ± 133.38	192.57 ± 99.87
Suboccipital (L)	211.16 ± 118.30	188.10 ± 84.58

M, male; F, female; HIT, Headache Impact Test; R, right; L, left; FMJ, first metacarpal joint; MT + E, Manual Therapy + Exercise.

(p < .001). Differences were also found in the GROC-Scale (p < .001) (Fig. 5).

In terms of self-treatment, 36.8% (MT + E) and 42.9% (Exercise) performed self-treatment every day, 15.8% (MT + E) and 33.3% (Exercise) between 4 and 6 days a week, 36.8% (MT + E) and 23.8% (Exercise) between 1 and 3 days a week, 10.5% (MT + E) and 0% (Exercise) less than 1 day a week. No differences were found between groups (p < .290).

4.3. 6-Month follow-up (T3)

In the within-group analysis of the exercise group (Table 2 and Fig. 4), only a statistically significant increase in the craniocervical flexion test was found (p < .001). In the MT + E group, we found statistically significant improvement in the headache intensity (p < .002), upper cervical spine flexion, HIT-6, right and left flexion-rotation test (p < .001) variables. A statistically significant increase was found in trapezius (right) (p < .021), C5-6 (right) (p < .015), suboccipital (right) (p < .007), trapezius (left) (p < .033), C5-6 (left) (p < .011), C2-3 (left) (p < .003) and suboccipital (left) (p < .001). There was also a statistically significant increase in the craniocervical flexion test (p < .001) (Fig. 4).

In the between-group analysis (Table 3), statistically significant differences were found between both groups in favor of the MT + E group in the headache intensity, upper cervical spine flexion, right and left flexion-rotation test (p < .001) variables, HIT-6 (p < .001), and in all PPT variables (p < .05). Differences were also found in the GROC-Scale (p < .001) (Fig. 5) and craniocervical flexion test variable (p < .038) (Fig. 4).

In terms of self-treatment, 10.5% (MT + E) and 14.3% (Exercise) performed self-treatment every day, 21.1% (MT + E) and 57.1% (Exercise) between 4 and 6 days a week, 57.9% (MT + E) and 28.6% (Exercise) between 1 and 3 days a week, 10.5% (MT + E) and 0% (Exercise) less than 1 day a week. Statistically significant differences were found between groups in favor of the exercise group (p < .048).

5. Discussion

Adding manual therapy to an exercise and home exercise protocol was better than an exercise protocol and home exercise in improving the symptoms and function of cervicogenic headache patients in the short- and mid-term follow-ups. This study showed statistically significant improvements in the flexion-rotation test in T1, T2, and T3 and upper cervical spine flexion during T2 and T3 follow-ups in the MT + E group. It is hypothesized that limited movement of any of the C0-1, C1-2, and C2-3 segments could limit the range of motion of the upper cervical spine due to its anatomical relationship with the alar ligament system [44,49]. In this study, translatoric manual therapy was applied in any upper cervical segment based on the segmental mobility findings and following international recommendations for security [50]. The improvement in flexion-rotation test was similar to previous studies in cervicogenic headache patients [4], cervicogenic dizziness [46], chronic neck pain [15], and hypomobile flexion-rotation test participants [44, 45].

In contrast, the exercise group did not experience statistically significant changes in upper cervical flexion and flexion-rotation test.

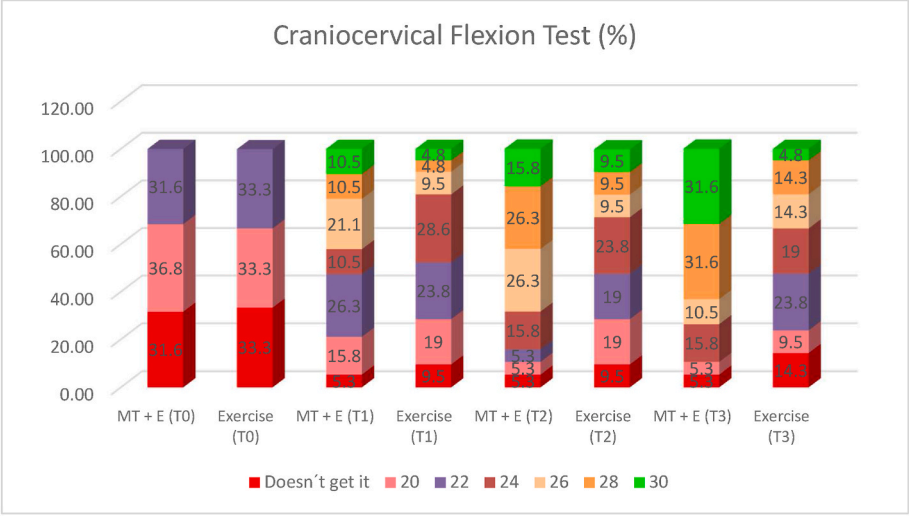

Fig. 4. Craniocervical flexion test graphic. Abbreviation: Mt + E, manual therapy + exercise.

Table 2
Outcomes variable values within-group.

		T0	T1				T2				T3			
		Baseline	1 Month	Difference between Baseline			3 Months	Difference between Baseline			6 Months	Difference between Baseline		
		Mean ± SD	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	d
Exercise Group	**Headache Intensity (cm)**	3.63 ± 2.28	3.45 ± 2.56	−0.18 ± 0.28	>1.000	0.07	4.50 ± 2.65	1.14 ± 0.37	>1.000	0.35	4.46 ± 2.96	0.83 ± 0.68	>1.000	0.31
	Upper Cervical Flexion (°)	10.52 ± 4.50	10.62 ± 5.61	0.10 ± 1.11	>1.000	0.02	9.19 ± 5.70	−1.33 ± 1.20	>1.000	0.26	9.10 ± 5.05	−1.42 ± 0.55	>.810	0.30
	HIT-6	56.33 ± 7.64	53.33 ± 10.23	−3.00 ± 2.59	>.207	0.33	56.14 ± 10.10	−0.19 ± 2.46	>1.000	0.02	56.33 ± 8.69	0.00 ± 1.05	>1.000	0.00
	Flexion-rotation test (R) (°)	17.68 ± 10.24	19.14 ± 12.33	1.56 ± 2.09	>1.000	0.13	15.33 ± 9.85	−2.35 ± 0.39	>1.000	0.23	15.71 ± 10.44	−1.97 ± 0.20	>1.000	0.19
	Flexion-rotation test (L) (°)	19.78 ± 10.62	21.19 ± 11.52	1.41 ± 0.90	>.963	0.14	15.71 ± 8.07	−4.07 ± 2.55	>.302	0.43	17.67 ± 11.85	−2.11 ± 1.23	>1.000	0.19
	Pressure Pain Threshold (Kpa)													
	First MCJ (R)	389.57 ± 193.87	368.86 ± 191.75	−20.71 ± 2.12	>1.000	0.11	324.95 ± 148.48	−64.62 ± 45.39	>.099	0.37	313.71 ± 132.02	−75.86 ± 61.85	>.100	0.46
	Trapezius (R)	207.43 ± 98.24	201.86 ± 88.75	−5.57 ± 9.49	>1.000	0.06	184.14 ± 86.62	−23.29 ± 11.62	>.769	0.25	186.67 ± 77.52	−20.76 ± 20.72	>1.000	0.24
	LS (R)	195.24 ± 118.47	163.71 ± 85.96	−31.53 ± 32.51	>.473	0.31	155.48 ± 86.62	−39.76 ± 31.85	>.354	0.38	163.05 ± 80.77	−32.19 ± 37.70	>.761	0.32
	C5-6 (R)	158.71 ± 71.04	154.57 ± 77.78	−4.14 ± 6.74	>1.000	0.06	137.67 ± 72.15	−21.04 ± 1.11	>.310	0.29	140.52 ± 70.38	−18.19 ± 0.66	>.886	0.26
	C2-3 (R)	187.19 ± 99.41	170.86 ± 89.80	−16.33 ± 9.61	>1.000	0.17	147.62 ± 82.56	−39.57 ± 16.85	>.118	0.43	147.62 ± 71.68	−39.57 ± 27.73	>.122	0.46
	Suboccipital (R)	193.14 ± 82.81	180.48 ± 90.92	−12.66 ± 8.11	>1.000	0.15	145.48 ± 78.33	−47.66 ± 4.48	**< .048**	0.59	154.10 ± 76.19	−39.04 ± 6.62	>.198	0.49
	First MCJ (L)	381.76 ± 176.15	358.81 ± 202.38	−22.95 ± 26.23	>1.000	0.12	345.14 ± 189.11	−36.62 ± 12.96	>1.000	0.20	324.57 ± 158.60	−57.19 ± 17.55	>.107	0.34
	Trapezius (L)	234.76 ± 103.30	212.00 ± 96.36	−22.76 ± 6.94	>1.000	0.23	203.86 ± 107.84	−30.90 ± 4.54	>.468	0.29	205.14 ± 89.13	−29.62 ± 14.17	>.554	0.31
	LS (L)	213.14 ± 134.94	184.48 ± 99.92	−28.66 ± 35.02	>.768	0.24	150.48 ± 89.38	−62.66 ± 45.56	**< .044**	0.55	162.00 ± 85.66	−51.14 ± 49.28	>.190	0.45
	C5-6 (L)	165.81 ± 80.62	157.57 ± 77.95	−8.24 ± 2.67	>1.000	0.10	135.57 ± 72.76	−30.24 ± 7.86	>.096	0.39	139.14 ± 62.86	−26.67 ± 17.76	>.305	0.37
	C2-3 (L)	192.57 ± 99.87	187.86 ± 91.77	−4.71 ± 8.1	>1.000	0.05	157.48 ± 88.84	−35.09 ± 11.03	>.084	0.37	169.52 ± 84.12	−23.05 ± 15.75	>.717	0.25
	Suboccipital (L)	188.10 ± 84.58	200.33 ± 88.74	12.23 ± 4.16	>1.000	0.14	166.14 ± 67.98	−21.96 ± 16.60	>1.000	0.29	167.24 ± 63.94	−20.86 ± 20.64	>1.000	0.28
Manual Therapy + Exercise Group	**Headache Intensity (cm)**	3.41 ± 1.94	1.04 ± 1.68	−2.37 ± 0.26	**< .006**	1.31	0.99 ± 1.50	−2.42 ± 0.44	**< .001**	1.40	1.19 ± 1.75	−2.22 ± 0.19	**< .002**	1,20
	Upper Cervical Flexion (°)	10.84 ± 4.45	13.32 ± 3.07	2.48 ± 1.38	>0.134	0.65	15.68 ± 4.49	4.84 ± 0.04	**< .010**	1.08	17.37 ± 4.39	6.53 ± 0.06	**< .001**	1.45
	HIT-6	57.22 ± 8.83	47.83 ± 9.62	−9.39 ± 0.79	**< .001**	1.02	47.17 ± 10.04	−10.05 ± 1.21	**< .001**	1.06	46.22 ± 9.58	−11.00 ± 0.75	**< .001**	1.19
	Flexion-rotation test (R) (°)	20.61 ± 11.17	41.42 ± 9.28	20.81 ± 1.89	**< .001**	2.03	38.32 ± 8.89	17.71 ± 2.28	**< .001**	1.75	36.95 ± 11.10	16.34 ± 0.07	**< .001**	1.47
	Flexion-rotation test (L) (°)	22.89 ± 8.17	40.47 ± 10.04	17.58 ± 1.87	**< .001**	1.92	38.47 ± 8.38	15.58 ± 0.21	**< .001**	1.88	38.26 ± 7.80	15.37 ± 0.37	**< .001**	1.92
	Pressure Pain Threshold (Kpa)													
	FMJ (R)	398.37 ± 221.50	386.37 ± 214.40	−12.00 ± 7.10	>1.000	0.06	408.00 ± 207.39	9.63 ± 14.11	>1.000	0.05	432.68 ± 221.79	34.31 ± 0.29	>1.000	0.16
	Trapezius (R)	213.90 ± 111.73	258.16 ± 148.86	44.26 ± 37.13	>.426	0.34	264.42 ± 126.78	50.52 ± 15.05	>.624	0.42	302.63 ± 146.00	88.73 ± 34.27	**< .021**	0.68
	LS (R)	218.89 ± 159.48	243.58 ± 112.39	24.69 ± 47.09	>1.000	0.18	276.05 ± 154.35	57.16 ± 5.13	>.630	0.36	305.21 ± 187.34	86.32 ± 27.86	>.227	0.50

(*continued on next page*)

Table 2 (*continued*)

	T0	T1				T2				T3			
	Baseline	1 Month	Difference between Baseline			3 Months	Difference between Baseline			6 Months	Difference between Baseline		
	Mean ± SD	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	d
C5-6 (R)	174.84 ± 95.23	212.26 ± 118.59	37.42 ± 23.36	>.342	0.35	236.79 ± 118.01	61.95 ± 22.78	**<.050**	0.58	269.68 ± 138.19	94.84 ± 42.96	**<.015**	0.80
C2-3 (R)	208.37 ± 132.09	245.16 ± 132.60	36.79 ± 0.51	>.841	0.28	274.58 ± 161.31	66.21 ± 29.22	>.239	0.45	308.16 ± 196.59	99.79 ± 64.50	>.063	0.60
Suboccipital (R)	216.89 ± 107.87	252.32 ± 121.73	35.43 ± 13.86	>.223	0.31	295.58 ± 130.71	78.69 ± 22.84	**<.006**	0.66	353.47 ± 202.47	136.58 ± 94.60	**<.007**	0.84
FMJ (L)	356.16 ± 214.81	373.76 ± 195.29	17.60 ± 19.52	>1.000	0.09	410.05 ± 200.47	53.89 ± 14.34	>1.000	0.26	471.47 ± 213.04	115.31 ± 1.77	>.131	0.54
Trapezius (L)	245.00 ± 132.36	312.89 ± 219.43	67.89 ± 87.07	>.248	0.38	303.11 ± 134.94	58.11 ± 2.58	>.186	0.44	345.21 ± 169.24	100.21 ± 36.88	**<.033**	0.66
LS (L)	230.58 ± 165.80	253.00 ± 155.37	22.42 ± 10.43	>1.000	0.14	278.11 ± 124.29	47.53 ± 41.51	>.699	0.32	315.84 ± 130.52	85.26 ± 35.28	>.139	0.57
C5-6 (L)	178.32 ± 87.77	233.53 ± 131.57	55.21 ± 43.80	>.197	0.49	257.11 ± 126.34	78.79 ± 38.57	**<.015**	0.72	291.58 ± 148.58	113.26 ± 60.81	**<.011**	0.93
C2-3 (L)	211.00 ± 133.38	279.47 ± 200.20	68.47 ± 66.82	>.110	0.40	300.42 ± 192.01	89.42 ± 58.63	**<.026**	0.54	337.63 ± 196.67	126.63 ± 63.29	**<.003**	0.75
Suboccipital (L)	211.16 ± 118.30	264.68 ± 133.36	53.52 ± 15.06	>.085	0.43	325.84 ± 178.77	114.68 ± 60.47	**<.002**	0.76	405.95 ± 234.79	194.79 ± 116.49	**<.001**	1.05

Abbreviation: SD, Standard Deviation; (R), Right; (L), Left; FMJ, First MetaCarpal Joint; LS, Levator Scapulae. Repeated Measures ANOVA was used. p values ≤ .05 are statistically significant.

Performing cervical exercises alone did not improve mobility function in our cervicogenic headache sample. These findings are similar to another study with patients with chronic neck pain and upper cervical spine restriction [15]. Our results support the benefits of adding manual therapy aimed at improving upper cervical spine mobility to an exercise protocol in cervicogenic headache patients too. Improving upper cervical spine mobility and symptoms seemed to favor the maintenance of improvement in T2 and T3. Studies have shown that this improvement may be maintained in the long-term for 1–3 years, even when the self-treatment after the initial treatment is inconsistent [14,51–53].

Regarding headache intensity, measured via headache intensity and HIT-6, statistically significant differences were found between both groups in favor of the MT + E group in the headache intensity in T1, T2, and T3 and in HIT-6 in T2 and T3. Similarly, patients' perception of improvement reflects a statistically significant improvement in the MT + E group compared to the exercise group in the GROC-Scale. The minimum clinically relevant difference from HIT-6 is established at 2.3 points [54] and in the headache intensity between 1 and 2 points [4,55]. The MT + E group showed a difference of 9.39 in T1, 10.05 in T2, and 11 points in T3 on the HIT-6 and 2.37 in T1, 2.42 in T2, and 2.22 in T3 on the headache intensity. These findings suggest that the application of manual therapy techniques aimed at the upper cervical spine and associated with cervical exercises may generate improvements in headache intensity and frequency.

Jull et al. (2002) showed positive results in headache intensity using cervical exercises in cervicogenic headache patients [14]. Our study's difference may be due to the inclusion criteria regarding positive flexion-rotation test and upper cervical spine segmental hypomobility. Other studies that have combined MT + E have found improvements in HIT-6 of 7.35 points at six months of follow-up [56] or 3.37 points in headache intensity [14]. These findings are similar to those found in our study in terms of headache intensity but are inferior in terms of the impact of headache on daily life (HIT-6). These results suggest part of the population of cervicogenic headache, especially those with upper cervical spine joint hypomobility, could be good responders to manual therapy application. This is in line with previous studies that observed positive results related to headache intensity [12], headache duration [12], headache frequency [57] and disability [58] in the management of cervicogenic headache with manual therapy. A recent clinical practice guideline also promoted patient-centred manual therapy as an adjunct therapy to exercise to treat patients with cervicogenic headaches [59].

In the craniocervical flexion test variable, we found statistically significant improvement in both groups in all follow-ups. Other studies have reported improvements in the craniocervical flexion test by applying manual therapy or MT + E techniques [14,60,61] or exercises [24,62], as both groups did in this study. MT + E group obtained greater improvements than the exercise group. Manual techniques aimed at the upper cervical spine may have the capacity to improve range of motion and the pattern of muscle recruitment. Jesús-Moraleida et al. showed better recruitment of the deep cervical muscles in this test after applying a mobilization directed to a cervical segment [63]. Falla et al. (2003) showed a linear relationship between the upper cervical spine range of motion and the contractile capacity of the deep cervical musculature [9].

Regarding the PPT, we found a statistically significant improvement in the MT + E group in T2, which is more evident in T3. On the contrary, in the exercise group, we found no statistically significant difference at any time. While a few studies did not find differences in the PPT applying manual therapy [4,64], others have found improvements in both the MT + E and exercise groups [65,66], and others found no between-group differences [62,67]. This contradictory result could suggest the population with cervicogenic headache does not respond similarly to the application of exercise or exercise associated with manual therapy. Our study suggests that adding manual therapy to exercise, compared to exercise alone, could be beneficial in cervicogenic headache patients with upper cervical spine hypomobility.

Table 3
Outcomes variable values between-group.

Variable	Group	T0	T1				T2				T3			
		Baseline	1 Month	Difference between Groups			3 Months	Difference between Groups			6 Months	Difference between Groups		
		Mean ± SD	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	D
Headache Intensity (cm)	E Group	3.63 ± 2.28	3.45 ± 2.56	2.41 ± 0.88	**< .001**	1.10	4.50 ± 2.65	3.51 ± 1.15	**< .001**	1.61	4.46 ± 2.96	3.27 ± 1.21	**< .001**	1.33
	MT + E Group	3.41 ± 1.94	1.04 ± 1.68				0.99 ± 1.50				1.19 ± 1.75			
Upper Cervical Flexion (°)	E Group	10.52 ± 4.50	10.62 ± 5.61	2.70 ± 2.54	<.071	0.59	9.19 ± 5.70	6.49 ± 1.21	**< .001**	1.26	9.10 ± 5.05	8.27 ± 0.66	**< .001**	1.74
	MT + E Group	10.84 ± 4.45	13.32 ± 3.07				15.68 ± 4.49				17.37 ± 4.39			
HIT-6	E Group	56.33 ± 7.64	53.33 ± 10.23	5.50 ± 0.61	<.094	0.55	56.14 ± 10.10	8.97 ± 0.06	**< .009**	0.89	56.33 ± 8.69	10.11 ± 0.89	**< .001**	1.11
	MT + E Group	57.22 ± 8.83	47.83 ± 9.62				47.17 ± 10.04				46.22 ± 9.58			
Flexion-rotation test (R) (°)	E Group	17.68 ± 10.24	19.14 ± 12.33	22.28 ± 3.05	**< .001**	2.03	15.33 ± 9.85	22.99 ± 0.96	**< .001**	2.44	15.71 ± 10.44	21.24 ± 0.66	**< .001**	1.97
	MT + E Group	20.61 ± 11.17	41.42 ± 9.28				38.32 ± 8.89				36.95 ± 11.10			
Flexion-rotation test (L) (°)	E Group	19.78 ± 10.62	21.19 ± 11.52	19.28 ± 1.48	**< .001**	1.78	15.71 ± 8.07	22.76 ± 0.31	**< .001**	2.77	17.67 ± 11.85	20.59 ± 4.05	**< .001**	2.03
	MT + E Group	22.89 ± 8.17	40.47 ± 10.04				38.47 ± 8.38				38.26 ± 7.80			
Pressure Pain Threshold (Kpa)												118.97 ± 89.77		
FMJ (R)	E Group	389.57 ± 193.87	368.86 ± 191.75	17.51 ± 22.65	<.787	0.09	324.95 ± 148.48	83.05 ± 58.91	<.151	0.46	313.71 ± 132.02		**< .044**	0.66
	MT + E Group	398.37 ± 221.50	386.37 ± 214.40				408.00 ± 207.39				432.68 ± 221.79			
Trapezius (R)	E Group	207.43 ± 98.24	201.86 ± 88.75	56.30 ± 60.11	<.150	0.47	184.14 ± 86.62	80.28 ± 40.16	**< .024**	0.75	186.67 ± 77.52	115.96 ± 68.48	**< .003**	1.01
	MT + E Group	213.90 ± 111.73	258.16 ± 148.86				264.42 ± 126.78				302.63 ± 146.00			
LS (R)	E Group	195.24 ± 118.47	163.71 ± 85.96	79.87 ± 26.43	**< .015**	0.72	155.48 ± 86.62	120.57 ± 67.73	**< .004**	0.98	163.05 ± 80.77	142.16 ± 106.57	**< .003**	1.00
	MT + E Group	218.89 ± 159.48	243.58 ± 112.39				276.05 ± 154.35				305.21 ± 187.34			
C5-6 (R)	E Group	158.71 ± 71.04	154.57 ± 77.78	57.69 ± 40.81	<.074	0.58	137.67 ± 72.15	99.12 ± 45.86	**< .002**	1.03	140.52 ± 70.38	129-16 ± 67.81	**< .001**	1.20
	MT + E Group	174.84 ± 95.23	212.26 ± 118.59				236.79 ± 118.01				269.68 ± 138.19			
C2-3 (R)	E Group	187.19 ± 99.41	170.86 ± 89.80	74.30 ± 42.80	**< .043**	0.66	147.62 ± 82.56	126.96 ± 78.75	**< .003**	1.01	147.62 ± 71.68	160.54 ± 124.91	**< .001**	1.11
	MT + E Group	208.37 ± 132.09	245.16 ± 132.60				274.58 ± 161.31				308.16 ± 196.59			
Suboccipital (R)	E Group	193.14 ± 82.81	180.48 ± 90.92	71.84 ± 30.81	**< .040**	0.67	145.48 ± 78.33	150.10 ± 52.38	**< .001**	1.41	154.10 ± 76.19	199.37 ± 126.28	**< .001**	1.33
	MT + E Group	216.89 ± 107.87	252.32 ± 121.73				295.58 ± 130.71				353.47 ± 202.47			
FMJ (L)	E Group	381.76 ± 176.15	358.81 ± 202.38	14.95 ± 7.09	<.813	0.08	345.14 ± 189.11	64.91 ± 11.36	<.299	0.33	324.57 ± 158.60	146.90 ± 54.44	**< .017**	0.79
	MT + E Group	356.16 ± 214.81	373.76 ± 195.29				410.05 ± 200.47				471.47 ± 213.04			
Trapezius (L)	E Group	234.76 ± 103.30	212.00 ± 96.36	100.89 ± 123.07	<.063	0.61	203.86 ± 107.84	99.25 ± 27.10	**< .014**	0.82	205.14 ± 89.13	140.07 ± 80.11	**< .002**	1.05
	MT + E Group	245.00 ± 132.36	312.89 ± 219.43				303.11 ± 134.94				345.21 ± 169.24			
LS (L)	E Group	213.14 ± 134.94	184.48 ± 99.92	68.52 ± 55.45	<.102	0.53	150.48 ± 89.38	127.63 ± 34.91	**< .001**	1.19	162.00 ± 85.66	153.84 ± 44.86	**< .001**	1.41

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Table 3 (*continued*)

Variable	Group	T0	T1				T2				T3			
		Baseline	1 Month	Difference between Groups			3 Months	Difference between Groups			6 Months	Difference between Groups		
		Mean ± SD	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	d	Mean ± SD	Mean ± SD	p value	D
	MT + E Group	230.58 ± 165.80	253.00 ± 155.37				278.11 ± 124.29				315.84 ± 130.52			
C5-6 (L)	E Group	165.81 ± 80.62	157.57 ± 77.95	75.96 ± 53.62	< **.031**	0.71	135.57 ± 72.76	121.54 ± 53.58	< **.001**	1.20	139.14 ± 62.86	152.44 ± 85.72	< **.001**	1.36
	MT + E Group	178.32 ± 87.77	233.53 ± 131.57				257.11 ± 126.34				291.58 ± 148.58			
C2-3 (L)	E Group	192.57 ± 99.87	187.86 ± 91.77	91.61 ± 108.43	<.066	0.60	157.48 ± 88.84	142.94 ± 103.17	< **.004**	0.97	169.52 ± 84.12	168.11 ± 112.55	< **.001**	1.13
	MT + E Group	211.00 ± 133.38	279.47 ± 200.20				300.42 ± 192.01				337.63 ± 196.67			
Suboccipital (L)	E Group	188.10 ± 84.58	200.33 ± 88.74	64.35 ± 44.62	<.078	0.57	166.14 ± 67.98	159.70 ± 110.79	< **.001**	1.21	167.24 ± 63.94	238.71 ± 170.85	< **.001**	1.42
	MT + E Group	211.16 ± 118.30	264.68 ± 133.36				325.84 ± 178.77				405.95 ± 234.79			

Abbreviation: E, Exercise; MT + E, Manual Therapy + Exercise; SD, Standard Deviation; (R), Right; (L), Left; FMJ, First MetaCarpal Joint; LS, Levator scapulae. One-way ANOVA was used. **p** values ≤ .05 are statistically significant.

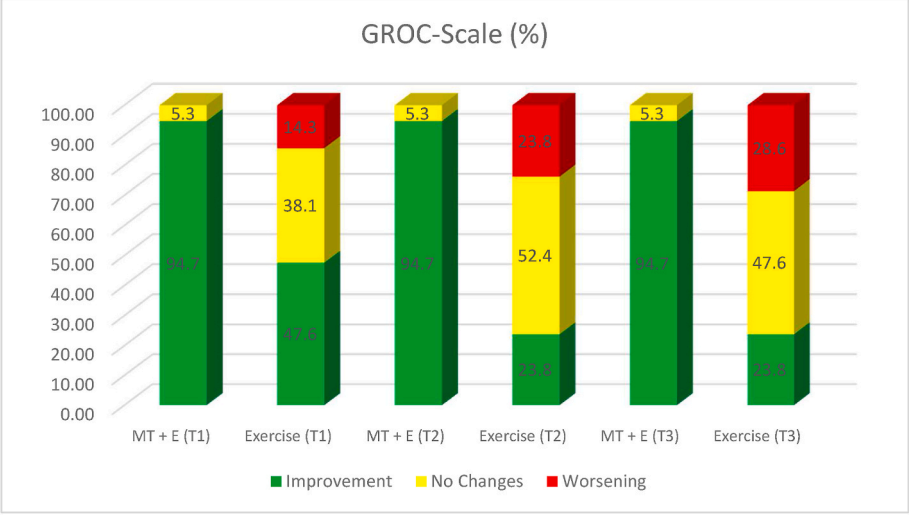

Fig. 5. Groc-scale graphic. Abbreviation: Mt + E, manual therapy + exercise.

The upper cervical spine region has a large number of mechanoreceptors in the suboccipital region [68–70]. It is interesting to note that the suboccipital region perceived the most significant improvements in this study compared to the rest of the points measured with PPT. This suggests there may be a relevant mechanical component in addition to the neurophysiological one [71].

6. Limitations

Manual diagnosis of segmental mobility, in our study, is based on the subjective judgment of a clinician with questionable inter-examiner reliability [19]. More research is needed to define cervicogenic headache subgroups with valid and generalizable inclusion criteria who respond best to a specific intervention. The exercise program, based on the contraction of deep neck flexor muscles, may not be the most appropriate to be performed without the support of manual therapy in these patients with headache and restriction of the upper cervical spine. Another relevant limitation is the representativeness of this subgroup of cervicogenic headache patients with upper cervical dysfunction among all the possible subgroups of patients with cervicogenic headache. Also, a single therapist provided the treatment to both groups, making decisions based on the clinical interpretation of the patients, which may limit the generalization of the results. Another limitation was that the ability to maintain quadrupedality was not taken into account in the exclusion criteria. Although all patients were able to maintain it, it is possible that some exercises performed in this position may have difficult the training of some patients. Finally, the selection of cervicogenic headache patients was based solely on clinical criteria. No anesthetic blocks were performed. These limitations should be considered for future studies. It is also advisable to select subgroups according to the different techniques used in this study to assess the isolated effectiveness of each in cervicogenic headache patients.

7. Conclusions

Performing four 20-min sessions of manual therapy and exercise protocol was more effective than applying only exercises in headache intensity, HIT-6, flexion-rotation test, craniocervical flexion test and GROC-Scale in the short term, and headache intensity, HIT-6, flexion-rotation test, upper cervical spine flexion, PPT, craniocervical flexion test, and GROC-Scale in the mid-term in cervicogenic headache patients.

Data availability statement and data deposition

You can find all the data from this study in the "HARVARD Dataverse" using the following link: https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/CGO1CT.

Funding sources

This study has no funding.

Ethical approval and registration details

This manuscript was registered in (Clinicaltrials.gov number: NCT04401501). This study complied with the ethical principles for medical research on human participants and was approved by the local ethics committee (CEICA; 13/2018).

Declaration of competing interest

The authors declare that there is no conflict of interest.

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