Research Article

Effects of Combining Diaphragmatic Exercise with Physiotherapy on Chronic Neck Pain: A Randomized Clinical Trial

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ABSTRACT

Introduction: Chronic neck pain (CNP) is of the most common symptoms of musculoskeletal disorder. Diaphragmatic exercises can reduce pain, and disability, improve proprioception, and correct forward head posture (FHP) in patients with CNP. The present study aims to determine the effect of combining diaphragmatic exercises with physiotherapy on pain, disability, and active range of motions of cervical and FHP in individuals with CNP.

Materials and Methods: Thirty women with CNP were randomly divided into two combined groups of diaphragmatic exercises and physiotherapy (DEPT) and PHYSIOTHERAPY ALONE (PT). Each person received ten sessions of treatment over two weeks. The results were assessed in the first and tenth sessions as well as two weeks later. Pain intensity was measured by visual analogue scale (VAS), disability by neck disability index (NDI), cervical active range of motions (CAROMs) by goniometry, and FHP by a lateral photograph.

Results: The VAS, neck disability index (NDI), CAROMs, and FHP were improved after the tenth session and in a two-week follow-up (P<0.001). A significant difference was observed between the groups for average changes of VAS (P=0.04) and active extension (P<0.001) after the tenth session, while the average changes between the two groups of cervical active left lateral flexion (P=0.82) and left rotation (P=0.11) in the next two weeks was not significant.

Conclusion: Both groups showed improvement in neck pain, disability, CAROMs, and FHP. However, diaphragmatic exercises and physiotherapy (DEPT) seem to have more lasting effects. Therefore, it is recommended to evaluate and modify the breathing patterns in the first line of treatment programs for patients with CNP.

Keywords:

Diaphragmatic exercise; Strength exercise; Pain; Chronic neck pain (CNP)

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1. Introduction

Chronic neck pain (CNP) is one of the most common symptoms of musculoskeletal disorder, which is included in the fourth category of debilitating problems [1, 2]. It is more common in women [3] and about 67% of people experience neck pain at least once during their lifetime [4]. Neck pain is especially common in specific occupations, such as employees [5, 6]. It is well known that persistent neck pain can cause negative effects in the biomechanics of the cervical spine. Sixty percent of patients with CNP have a forward head posture (FHP) which increases pressure on the posterior structures of the neck and increases muscle activity, such as sternocleidomastoid muscle (SCM) and scalene, which can cause referral pain in the upper extremity [7]. Furthermore, a significant relationship is observed between increased FHP and decreased respiratory muscle strength in a patient with CNP. These patients have features, such as decreased activity of neck muscles, such as deep neck flexors, increased activity and fatigue in the superficial flexor muscles, such as SCM, restriction of range of motion, increased FHP, and pain intensity [8]. It is well established that the proximity of the ribs and pelvic increases intra-abdominal pressure in subjects with kyphotic posture, which can lead to respiratory dysfunction [9]. The diaphragm is a dome-shaped muscle and is vital in postural stability and respiration [10]. Briefly, changing the movement pattern of the diaphragm can lead to decreased lung volume, hypoxia, respiratory alkalosis, and increased irritability of the central and peripheral nervous system, which is a negative cycle that again disrupts the normal rhythm of respiration [11]. So far, the effect of stretching, strengthening, and endurance exercises in patients with CNP have been studied and it has been effective in reducing pain, disability, coordination between deep and superficial flexor muscles, and normalization of cervical lordosis [12-14].

Changes following CNP include decreased respiratory capacity and weakness of the respiratory muscles [15]. These people use the chest breathing pattern, in which the sternum moves vertically upward instead of forward in the transverse plane during inspiration [16]. The previous findings showed that training in correct breathing in patients with the postural disorder can improve respiratory function, chest mobility, and stability of the neck and thoracic spine [17-20]. According to a study, diaphragmatic exercise alone reduces pain, and disability, improves proprioception, and corrects FHP in patients with CNP [21]. On the other hand, Mohan et al. showed that 8 weeks of physiotherapy and breathing exercises in patients with neck pain reduced pain, while the CROMs was not significantly different between groups [18].

To our knowledge, little information is available about the long-term effects of the combination of Diaphragmatic Exercises And Physiotherapy (DEPT) in a patient with CNP. Therefore, the present study aims to compare the effect of DEPT and physiotherapy alone (PT) on pain intensity, disability, Cervical Active Range of Motions (CAROMs), and FHP in the tenth session and two weeks later in patients with CNP.

2. Materials and Methods

The study was a randomized clinical trial (RCT ID: IRCT20210223050476N1). Thirty women aged (20-35) years with CNP were recruited for the study. The individuals were referred by physicians to the physiotherapy clinic at the School Rehabilitation, Tehran University of Medical Sciences (TUMS). At the tenth session and two weeks later, none of the subjects were excluded from the study. None of the participants used any specific medication during the study.

All subjects read and signed informed consent before commencing the study. Also, ethical approval of the study was granted by Ethics Committee at the Tehran University of Medical Sciences (TUMS) (IR.TUMS.FNM.1399.114).

The inclusion criteria included women with CNP for at least 3 months in the posterior neck to the beginning of the thoracic area with or without pain in the shoulder girdle [22], with cranial vertebral angle (CVA)<49° [23], Visual analogue scale (VAS) ≥3 for pain intensity [22], paradoxical breathing and no physiotherapy in the last 3 months for neck pain [21]. The exclusion criteria included the feeling of discomfort and intolerance of treatment by the patients, congenital abnormality of the spine, such as scoliosis, history of neck injury, diabetes, body mass index (BMI)>40 [1], cervicogenic headache, acute neuromuscular pain, cervical herniated disc with neurological symptoms and other sensory disorders, history of heart disease and surgeries, smoking, and pregnancy.

Participants were randomly divided in two groups of the DEPT and PT using online randomization [24]. The evaluator and the randomizer were blinded to group allocation. The variables were evaluated by an assessor who was not aware of the grouping.

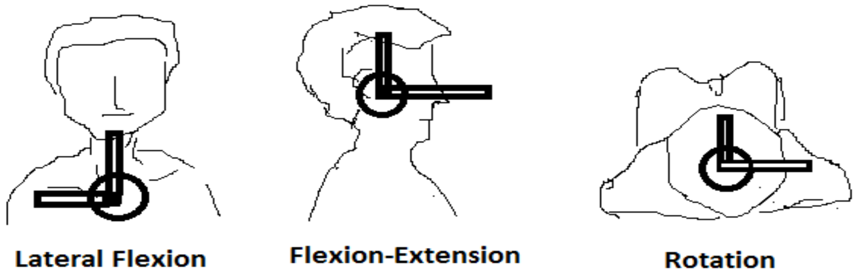

Figure 1. Measuring the Cervical Active Range of Motion (CAROM) by goniometer

First, characteristics and initial examinations were measured and recorded by an experienced therapist. Then, the pain intensity was measured by VAS, activity limitation for neck pain by neck disability index (NDI), CAROM of all movements by goniometry, and FHP by the lateral photograph and recorded at the baseline. VAS ranges from 0 to 10 cm and a higher score indicates unbearable pain [25].

Persian version of NDI is composed of 10 parts, 7 parts related to daily life activities, 2 parts related to the intensity of pain, and 1 part related to concentration [26, 27]. A calibrated goniometer (NOAVARAN, Model SH5203) was used to measure the CAROM of all movements (Figure 1) [28]. The subject sat on a chair in a comfortable position with a straight face, the knees positioned at 90°, both feet rested flat on the floor and their arms were positioned at their side. The patients were asked to perform two repetitions for each cervical motion and the average score was recorded for each motion. FHP measurement FHP method was based on Falla's study [29]. The patient sat on the chair. A Tablet (Samsung Galaxy Tab A SM-T355, 5 MP Camera, made in South Korea) was placed on a tripod at a distance of 0.8 m. The lens axis of the camera was perpendicular to the sagittal plane and along the seventh cervical vertebrae (C7). The markers were placed on the lateral canthus of the eye, tragus of the ear, and spinous process of C7. The cranial rotational angle (CRA) is evaluated between the line connecting the lateral canthus of the eye, the tragus of the ear, and a horizontal line passing through the tragus. The CVA evaluated between the line connecting the tragus, the spinous process of C7, and a horizontal line passing through the C7 (Figure 2). Pain intensity, disability, and FHP were measured once and the CAROMs was measured twice in each of the first, and tenth sessions and two weeks later. All variables were measured in the first, and tenth sessions and two weeks later.

The DEPT group received diaphragmatic exercise and physiotherapy.

The diaphragmatic exercise was performed in a supine position with 40° trunk flexion (Figure 3) while holding 2.5 kg on the abdomen in the first 5 sessions and then 5

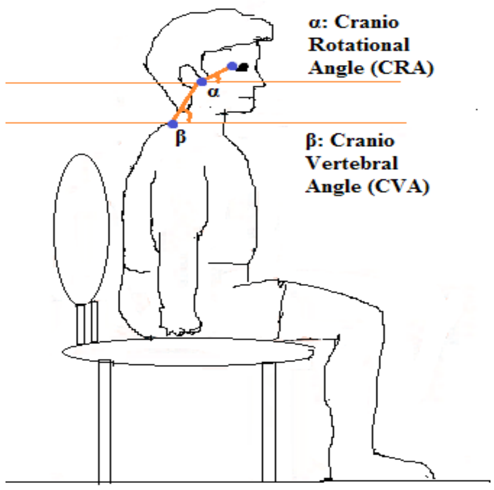

Figure 2. Measurement of head and cervical posture in sagittal plane

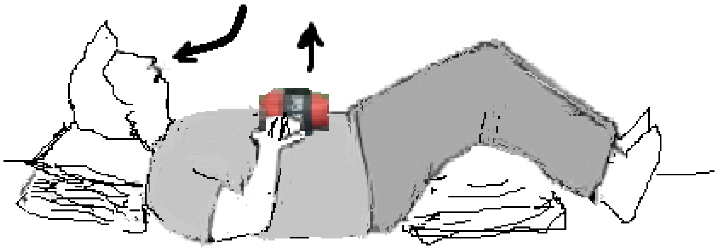

Figure 3. Diaphragmatic exercise with weight

kg in the second 5 sessions. Participants performed 3 sets with 10 repetitions at a ratio of one second of inspiration to two seconds of expiration, three sets of 15 repetitions at a ratio of two seconds of inspiration to four seconds of expiration, and three sets of 20 repetitions at a ratio of three seconds of inspiration to six seconds of expiration. The rest between rests was 60 s. These exercises were performed 5 days a week in 10 sessions [30].

Physiotherapy included Transcutaneous Electrical Nerve Stimulation (TENS) on the painful regions around the neck for 30 minutes with a TENS device (NOVIN, Model 735X). TENS parameters were 150 µs square pulses with a frequency of 80 Hz [31]. The intensity of the current was adjusted to produce no contraction. Infrared (TAVANBAKHSHNOVIN, Model Single Lamp Unit) was used on the neck and back for 20 minutes each session [32]. The lamp was placed at a distance from the patient's body to create a good feeling in the person and two types of strength and stretching exercises (The strength exercise included the chin tuck head lift exercise (Figure 4) [33]. In the first 5 sessions, the subjects had tucked the chin and lifted the head off the table inclined at a 60° angle. When the patient held this position for 10 seconds, the inclination angle of the table gradually decreased by 10°, and the holding sequence was repeated for 10 s. This exercise was performed until the inclination angle of the table reached 30°. In the second 5 sessions, the participants had tucked the chin and lifted the head off the table inclined at 30° angle. Similar to the previous exercise, the inclination angle of the table progressively decreased by 10° and this exercise was performed until the inclination angle of the table reached 0°. This exercise was performed ten times in each of the four angles and Stretching Exercises (SCM and upper trapezius [UT] stretching exercises were carried out for 30 s with repetition 3 times per session while the person was sitting on a chair with both feet resting flat on the floor) [34].

PT group received physiotherapy alone (similar to the physiotherapy of the DEPT group). The duration of each session in the two groups was 60 to 70 minutes.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 26.0 software (IBM Corp, Armonk, NY). The Shapiro-Wilk was utilized to test the data distribution of numerical variables. The central tendency and dispersion indices were used to describe the numerical variables. Moreover, to compare disability, CAROMs, and FHP in the groups, we used repeated measures analysis of variance due to their normal distribution and the Friedman test for pain intensity considering its non-normal distribution. Furthermore, the independent t-test for parametric data and Mann-Whitney U test for non-parametric data were used to compare the changes in variables between the groups.

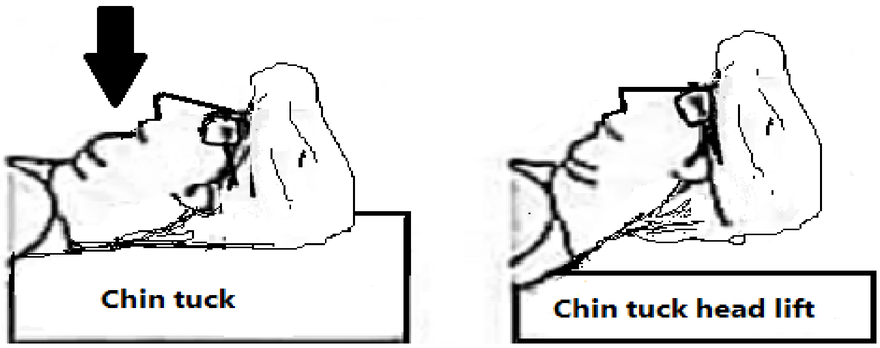

Figure 4. Chin tuck head lift exercise

3. Results

The participants in the DEPT group (15 females, aged: 27.80±2.83 years, height: 165.14±1.95 cm, weight: 71.43±6.89 kg, BMI: 26.21±2.76, duration of neck pain: 27.67±6.46 months) did not differ significantly from the subject in the PT group (15 females, aged: 27±2.61 years, height: 164.75±1.84 cm, weight: 73.35±5.09 kg, BMI: 27.05±2.19, duration of neck pain: 29.87±7.62 months) in age, weight, height, BMI and duration of neck pain (P>0.05)

In the first session, all variables were not significantly different between the groups (P>0.05). Table 1 presents the values (Mean±SD) of variables in the first, and tenth sessions and two weeks later. The results of the Shapiro-Wilk test showed that the pain intensity of the control group did not have a normal distribution. Statistical evaluations to compare within-group variables showed that both groups decreased significantly in VAS (P<0.05), NDI (P<0.001), and CRA (P<0.001) and significantly increased in their CVA (P<0.001) and CAROMs (P<0.001) after the tenth session and two weeks later than the first session (Table 2). However, the results

Table 1. Descriptive statistics of variables in both groups (n=15)

Variables	Intervention	Mean±SD		
		First Session	Tenth Session	Two Weeks Later
VAS (cm)	DEPT	6.21±0.69	3.30±0.51	3.41±0.68
	PT	6.39±0.80	3.82±0.74	4.56±0.76
NDI	DEPT	29.93±4.18	13.86±2.47	14.93±3.49
	PT	28.80±6.07	14.13±3.66	16.60±4.20
AFLX (degree)	DEPT	40.21±6.66	51.71±5.71	51.55±5.75
	PT	41.20±6.23	51.55±5.36	48.58±5.26
AEXT (degree)	DEPT	34.46±3.68	46.45±3.99	44.90±4.01
	PT	33.48±4.67	43.31±4.48	40.33±5.07
ALatFlxR (degree)	DEPT	31.76±3.90	41.25±3.17	39.63±4.82
	PT	31.38±3.48	40.41±3.27	37.33±3.89
ALatFlxL (degree)	DEPT	32.01±3.64	44.13±3.45	42.91±4.62
	PT	32.66±4.21	43.73±4.47	42.66±4.72
ARotR (degree)	DEPT	48.11±4.30	60.55±5.37	59.33±6.10
	PT	48.80±4.27	59.50±5.70	56.80±6.06
ARotL (degree)	DEPT	49.65±4.87	63.88±4.99	63.81±5.41
	PT	50.56±4.97	63.31±5.28	62.21±5.11
CRA (degree)	DEPT	32.68±5.13	29.17±5.03	29.79±5.40
	PT	31.87±6.09	28.52±6.06	30.14±5.98
CVA (degree)	DEPT	39.92±3.76	44.06±3.67	43.85±3.49
	PT	39.23±4.65	43.05±4.76	41.68±4.83

JMR

VAS: Visual analog scale; NDI: Neck disability index; AFLX: Active flexion; AEXT: Active extension; ALatFlxR: Active lateral flexion to right; ALatFlxL: Active lateral flexion to left; ARotR: Active rotation to right; ARotL: Active rotation to left; CRA: Cranial rotation angle; CVA: Cranial vertebral angle; DEPT: Diaphragmatic exercise and physiotherapy; PT: Physiotherapy alone.

Table 2. Statistical tests and results to compare variables within the groups (n=15)

Variables	Intervention	Statistical Test	df	F	P: First Session With Tenth Session	P: First Session With Two Weeks Later	P: Tenth Session With Two Weeks Later	Effect Size
VAS (cm)	DEPT	Repeated measurement analysis	2	534.94	< 0.001*	<0.001*	0.63	0.97
	PT	Friedman test	2		< 0.001*	0.006*	0.006*	1
NDI	DEPT	Repeated measurement analysis	1.43	294.03	< 0.001*	<0.001*	0.10	0.95
	PT	Repeated measurement analysis	1.12	127.92	< 0.001*	<0.001*	< 0.001*	0.90
AFLX (degree)	DEPT	Repeated measurement analysis	2	167.28	< 0.001*	< 0.001*	1.00	0.92
	PT	Repeated measurement analysis	1.11	184.78	< 0.001*	<0.001*	< 0.001*	0.93
AEXT (degree)	DEPT	Repeated measurement analysis	1.29	349.48	< 0.001*	<0.001*	0.047*	0.96
	PT	Repeated measurement analysis	2	211.24	< 0.001*	<0.001*	< 0.001*	0.94
ALatFlxR (degree)	DEPT	Repeated measurement analysis	2	175.51	< 0.001*	<0.001*	0.033*	0.92
	PT	Repeated measurement analysis	2	419.42	< 0.001*	<0.001*	< 0.001*	0.96
ALatFlxL (degree)	DEPT	Repeated measurement analysis	2	254.74	< 0.001*	<0.001*	0.069	0.95
	PT	Repeated measurement analysis	2	405.71	< 0.001*	<0.001*	0.084	0.97
ARotR (degree)	DEPT	Repeated measurement analysis	2	195.75	< 0.001*	<0.001*	0.16	0.93
	PT	Repeated measurement analysis	1.24	203.27	< 0.001*	<0.001*	< 0.001*	0.95
ARotL (degree)	DEPT	Repeated measurement analysis	2	470.30	< 0.001*	<0.001*	1.00	0.97
	PT	Repeated measurement analysis	1.24	280.99	< 0.001*	<0.001*	0.073	0.95
CRA (degree)	DEPT	Repeated measurement analysis	2	53.45	< 0.001*	<0.001*	0.15	0.79
	PT	Repeated measurement analysis	2	64.44	< 0.001*	<0.001*	< 0.001*	0.82
CVA (degree)	DEPT	Repeated measurement analysis	2	98.97	< 0.001*	<0.001*	1.00	0.87
	PT	Repeated measurement analysis	2	116.32	< 0.001*	<0.001*	< 0.001*	0.89

JMR

VAS: Visual analog scale; NDI: Neck disability index; AFLX: Active flexion; AEXT: Active extension; ALatFlxR: Active lateral flexion to right; ALatFlxL: Active lateral flexion to left; ARotR: Active rotation to right; ARotL: Active rotation to left; CRA: Cranial rotation angle; CVA: Cranial vertebral angle; DEPT: Diaphragmatic exercise and physiotherapy; PT: Physiotherapy alone.

Table 3. Statistical tests and comparison of the mean changes of each variable between groups (n=15)

Variables	Intervention Session	Statistical Test	P	Effect Size
VAS changes (cm)	Tenth session	Independent t-test	0.04*	0.35
	Two weeks later	Independent t-test	<0.001*	0.76
NDI changes	Tenth session	Mann-Whitney U test	0.61	0.008
	Two weeks later	Independent t-test	0.023*	0.40
AFLX changes (degree)	Tenth session	Independent t-test	0.25	0.20
	Two weeks later	Independent t-test	<0.001*	0.66
AEXT changes (degree)	Tenth session	Independent t-test	<0.001*	0.63
	Two weeks later	Independent t-test	0.049*	0.35
ALatFlxR changes (degree)	Tenth session	Independent t-test	0.44	0.13
	Two weeks later	Independent t-test	0.028*	0.39
ALatFlxL changes (degree)	Tenth session	Independent t-test	0.18	0.24
	Two weeks later	Independent t-test	0.82	0.042
ARotR changes (degree)	Tenth session	Independent t-test	0.052	0.35
	Two weeks later	Independent t-test	0.031*	0.39
ARotL changes (degree)	Tenth session	Independent t-test	0.052	0.35
	Two weeks later	Mann-Whitney U test	0.11	0.08
CRA changes (degree)	Tenth session	Independent t-test	0.72	0.06
	Two weeks later	Mann-Whitney U test	0.033*	0.15
CVA changes (degree)	Tenth session	Independent t-test	0.39	0.15
	Two weeks later	Independent t-test	0.005*	0.48

JMR

VAS: Visual analog scale; NDI: Neck disability index; AFLX: Active flexion; AEXT: Active extension; ALatFlxR: Active lateral flexion to right; ALatFlxL: Active lateral flexion to left; ARotR: Active rotation to right; ARotL: Active rotation to left; CRA: Cranial rotation angle; CVA: Cranial vertebral angle; DEPT: Diaphragmatic exercise and physiotherapy; PT: Physiotherapy alone.

of repeated measures analysis of variance two weeks later compared to the tenth session of NDI, CRA, CVA, and CAROMs in the PT group showed a significant decrease in CVA (P<0.001), CAROM of all movements except the left rotation (P=0.073) and left lateral flexion (P=0.084) and a significant increase in NDI (P<0.001), and CRA (P<0.001). Based on the results of the Friedman test in the PT group, the pain intensity showed a significant increase two weeks later compared to the tenth session (P=0.006) (Table 2).

The results of the independent t-test for VAS, CRA, CVA, and CAROMs and Mann-Whitney U test for NDI showed no significant difference between groups for average changes of each variable in the tenth session except in VAS (P=0.04) and, CAROM of extension (P<0.001). The statistical evaluation of the independent t-test for VAS, NDI, CVA, and CAROMs of all movements except cervical left rotation and Mann-Whitney U test for cervical left rotation and CRA showed a significant difference between groups for average changes of VAS (P<0.001), NDI (P=0.023), CRA (0.033), CVA (P=0.005), CAROM of all movements except the cervical left rotation (P=0.11) and left lateral flexion (P=0.82) in two weeks later (Table 3).

4. Discussion

This study aimed to compare the effect of adding diaphragmatic exercise to physiotherapy treatment on pain, disability, CAROMs, and FHP in patients with CNP. The results showed no significant difference between the

DEPT and PT groups for average changes of NDI, CRA, CVA, and all of the CAROMs except pain intensity and cervical extension in the tenth session. Other important findings of this study were a significant difference in all variables except CAROMs of left rotation and left lateral flexion between the groups two weeks later.

According to Comerford and Mottram (2012), prolonged pain in patients with CNP during a defective cycle causes limitation of movement and muscle weakness in these people [35]. So far, the effects of TENS, stretching, and strengthening exercises in patients with CNP have been studied and found to be effective in reducing pain, disability, and CROMs [12, 13, 32]. In our study, all the variables of the PT group showed significant changes in the tenth session compared to before treatment, while two weeks later, no significant changes were observed in cervical left rotation and left lateral flexion compared to the tenth session. Regarding the pain intensity and disability, the results of our study were consistent with the studies conducted by Chuitt et al. and Escortell et al. in which exercise and TENS were compared in a patient with CNP [31, 32]. The results of the comparison showed that exercise and TENS had a significant effect on improving pain and disability.

Most patients with CNP have FHP [7]. Regarding the FHP and CAROM, the present results were consistent with the research by Chung et al. [36]. According to that study, cranial vertebral exercise (CVE) significantly improved FHP compared to neck isometric exercise. Although some differences existed in the type and number of exercises and they had no follow-up. The present study performed progressive CVE by chin tuck head lift exercise in ten sessions. According to the previous studies, the mechanism of improvement of FHP by exercise was probably the reduction of activity of UT and SCM [37]. However, most patients with CNP have abnormal breathing patterns, which change the diaphragm movement pattern and reduce respiratory capacity [15, 16]. Changing the movement pattern of the diaphragm can lead to decreased lung volume, increased activity, and fatigue in the superficial flexor muscles of the neck, such as SCM and increased irritability of the central and peripheral nervous system, which is a negative cycle that again disrupts the normal rhythm of respiration [11]. So far, many findings have shown that the training of correct breathing in patients with the postural disorder can improve respiratory function, chest mobility, and stability of the neck and thoracic spine [17-20]. According to previous studies, diaphragmatic training added to the therapeutic exercise significantly improved pain intensity, CROMs, the function of the diaphragm muscle, erector spinae activity of the neck, and respiratory rate [18, 37]. In our study, all variables in the DEPT group showed significant changes in the tenth session compared to before treatment, while two weeks later, significant changes were observed in cervical extension and right lateral flexion compared to the tenth session. The findings of the present study were consistent with the former study by Alvandi et al. [21], who found the effects of diaphragmatic exercise in the patient with CNP can decrease the pain intensity, disability, CVA and increase cervical proprioception. However, Alvandi et al. only used diaphragmatic training for 8 weeks and did not follow the parameters after the treatment sessions. Furthermore, Mohan et al. applied routine physiotherapy and respiratory exercises to treat neck pain for 8 weeks [18]. This study indicated that 8 weeks of physiotherapy and breathing exercises in patients with neck pain reduced pain, while the CROMs was not significantly different between groups. The difference in results between the study and our research may be due to the small sample size of the study, the type of breathing exercise (diaphragmatic exercise with pursed-lips breathing without using weight on the abdomen), and did not follow the parameters after the treatment.

The results of our study showed that ten sessions of interventions DEPT significantly improved VAS, NDI, CAROMs, and FHP in patients with CNP and the effects lasted at least two weeks after the last session.

Studies of the effects of diaphragm exercise showed that diaphragmatic training can help facilitate slow breathing, and relaxation and reduce stress [38]. Mourya et al. observed the slow breathing effect on autonomic system [39]. So that studies of diaphragm analysis during inhalation and exhalation by ultrasonic waves showed that slow, deep, and controlled breathing exercises greatly improve pulmonary ventilation, increase arterial oxygen volume and modulate the function of the sympathetic system [40, 41].

According to studies mentioned above for the effectiveness of diaphragmatic exercise, it seems that combined diaphragmatic exercises and physiotherapy treatment have more lasting effects to improve the patients with CNP. Since diaphragmatic training is a non-invasive and safe method that helps people to be aware of their posture and respiratory pattern, therefore, it is recommended to evaluate and modify the breathing pattern in the first line of treatment programs for patients with CNP.

The status of the COVID-19 pandemic was one of our limitations of face-to-face access to patients. The lack of a diaphragmatic exercise group alone due to medical ethics issues was the other limitation.

It is suggested to use an equal number of male and female volunteers in the treatment of groups in future studies, while the participants are blind to the type of treatment in each group.

5. Conclusion

Both groups showed improvement in neck pain, disability, CAROMs, and FHP. However, DEPT seems to have more lasting effects. Therefore, it is recommended to evaluate and modify the breathing patterns in the first line of treatment programs for patients with CNP.

Ethical Considerations

Compliance with ethical guidelines

The research project was ethically approved by the Tehran University of Medical Sciences (TUMS) (Code: IR.TUMS.FNM.1399.114).

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Authors' contributions

All authors equally contributed to preparing this paper.

Conflict of interest

The authors declared no conflict of interest.

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