# A protocol for a randomized trial on pain neuroscience education vs. routine physical therapy in people with chronic neck pain

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***Abstract***

The aim of this study is to investigate the effects of combining routine physical therapy with pain neuroscience education (PNE) on psychosocial factors, physical performance, and the experienced pain in patients with chronic neck pain (CNP). This study is a double-blind randomized clinical trial in which patients will be randomly allocated to two groups, routine physical therapy with and without PNE. Patients will be assessed at the baseline, post intervention, and three months later. The results of this research will be used to establish effectiveness of treatment strategies for CNP. Due to the rigorous scientific methods used in this research, the suggested interventions would be clinically applicable in the health care systems.

**Key Words**: Chronic neck pain; pain neuroscience education; psychosocial factors; physical therapy.

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Neck pain is a major public health worldwide which interferes with daily life and can lead to depression and anxiety.[1]

The majority of the neck pain disorders are often non-specific in nature, meaning that there is either no tissue damage or the tissue damage is not severe enough to explain the associated symptoms.[2]

Central sensitization (CS)[3] is a physiological process in chronic pain patients that results in an increase in the responsiveness of pain neurons in the central nervous system to the entry of natural or sub-threshold afferents.[4]

However, if CS persists, it becomes maladaptive and can facilitate the maintenance of symptoms such as pain in the absence of tissue damage or illness. If this occurs, CS can be viewed as a pathophysiological process, which negatively impacts treatment outcome.

In this view, it seems rational to consider treating CS.[5,6]

Chronic neck pain (CNP) is one of the conditions in which CS was seen in a subgroup of patients. A study by Roldan-Jimenez et al. (2020)[7] confirmed CS in 33% of patients with CNP.

In recent evidence, a therapeutic approach, named pain neuroscience education (PNE) has been recommended in care for individuals with chronic musculoskeletal conditions.[8-10]

PNE consists of educational sessions describing the neurobiology and neurophysiology of chronic pain and pain processing. Some researchers have reported the possibility of improving the effects of treatment with PNE in patients with chronic musculoskeletal pain. For example, one study has shown that 2 sessions of PNE improve pain in fibromyalgia patients.[8] Meeus et al. also showed that Pain physiology education has been able to change the perception of pain, such as pain catastrophe in chronic musculoskeletal pain.[9,10]

As far as we know, there is little evidence examining the role of combining PNE with routine physical therapy for CNP versus simple routine physical therapy. Therefore, the purpose of this study is to compare the effectiveness of combining PNE with routine physical therapy for CNP with routine physical therapy alone. We hypothesized that PNE could lead to improvement in psychosocial measures, functionality and pain in patients with CNP.

## Materials and Methods

*Study Design*

This proposed study is a double-blind, parallel-group, randomized control. This study protocol report follows the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline.[11] In addition, specific interventions were described based on the Template for Intervention Description and Replication (TIDieR) checklist,[12] and the Consensus on Exercise Reporting Template (CERT) checklist.[13] The trial has been approved by the ethics committee of Ahvaz Jundishapur University of medical sciences (Ethical number: IR.AJUMS.REC.1400.098). The trial identifier code is IRCT20210607051508N1 and it was registered on June 21, 2021.

*Participants and Setting*

Patients will be recruited from the physical therapy clinics located in Ahvaz, Iran. The participants will be included according to the following inclusion criteria: age from 18 to 65,[14] diagnosis of nonspecific neck pain [pain in cervical region that provokes by sustained neck postures or particular neck movements with no specific pathological finding],[15] history of pain greater than twelve weeks, ability to comprehend, speak, and write in Persian, not being under any other treatments up to 6 months prior to the study, visual analog scale (VAS) at least 30 out of 100, the Central Sensitization Inventory (CSI) score of above 40. The exclusion criteria are a history of malignancies, fractures, metabolic, rheumatism, cardiovascular, or neurologic disorders, neck pain due to radiculopathy, myelopathy, accompanied by headache, patients with generalized pain disorders such as fibromyalgia and chronic fatigue syndrome.[16,17]

*Sample Size*

The sample size was calculated using the G power software, version 3.1.10. Applying a significance level of 0.05, effect size of 0.8, and a power of 80%, the calculation revealed that 22 patients would be required in each group. Since a 10% patients loss due to follow-up is presumed, a total of 25 patients will be included in each group.

*Randomization and allocation concealment*

Individuals who met the inclusion criteria will randomly be allocated to one of two treatment arms: (1) routine physical therapy plus PNE or (2) Routine physical therapy, using computer-generated random numbers in stratified permuted block (block size of 4 and 6). The allocation will be concealed in an opaque, sealed envelope. A research assistant opens them and assigns patients to either of the treatment arms. The randomization will be conducted after signing the informed consent and baseline assessments. Demographic measures include gender, age, height, weight, and comorbidities.

*Interventions*

The recruitment is announced for patients with nonspecific CNP from public physical therapy clinics, and the screening will be based on the predefined inclusion and exclusion criteria. The participants will be evaluated before, after the intervention, and three months later. Treatment will be performed by one expert physical therapist. Both intervention groups will receive 12 sessions, 3 times a week.

Routine physical therapy group:

All subjects received the routine exercise program consist of 20 minutes TENS (Novin, model 733x), hot packs, stretching of pectoralis minor, pectoralis major, latissimus dorsi, upper trapezius and scalene muscles, deep neck flexor muscle training by a stabilizer instrument, strengthening exercises (using Thera-Band and Dumbbells for deep neck extensors and scapular stabilizer muscles).

Routine plus PNE physical therapy group:

PNE will be conducted in four consecutive sessions, held in four separate meetings. The first session will be dedicated to elaborating the physiology of pain, the concepts of neurons, synapses, and neural facilitation and inhibitions. Also, the nature of acute versus chronic pain and the concept of neural plasticity will be presented. At the end of the first session, patients will be provided with a booklet elaborating on this information. The second session will be dedicated to teaching the neurophysiology of pain and cortical mechanisms in pain modulation. The educator in this session will attempt to walk the patients through the neuroscience of pain and change their preconceived notions in this regard. Reading assignments are considered to be fulfilled between the first and second sessions alongside practical tasks designed based on appropriate target goals. The third and fourth meeting is dedicated to cognition targeted exercise therapy. At the third session, patients will be instructed to cognition targeted motor control training. In this session, it will be clarified for the patients that the essential objective of this training is cognitive reeducation and the instructed exercises are not directly in favor of reducing their pain. This goal will be attained using an appropriate interview with the patient. Ten exercises will be assigned in each session with 10 seconds breaks between the sessions, and the exercises will initiate from those provoking less avoidance and will proceed to those with stronger avoidance. Eventually, the last session is dedicated to cognition-targeted dynamic and functional exercises, consisting of time contingent neuromuscular training rather than symptom-oriented training. Gradual exposure will be applied in all training to avoid potential hazards. Motor imaging techniques will be instructed and required before each task, and functional interaction between the trainer and trainee is mandatory for full filling this step. The objective in this last step is

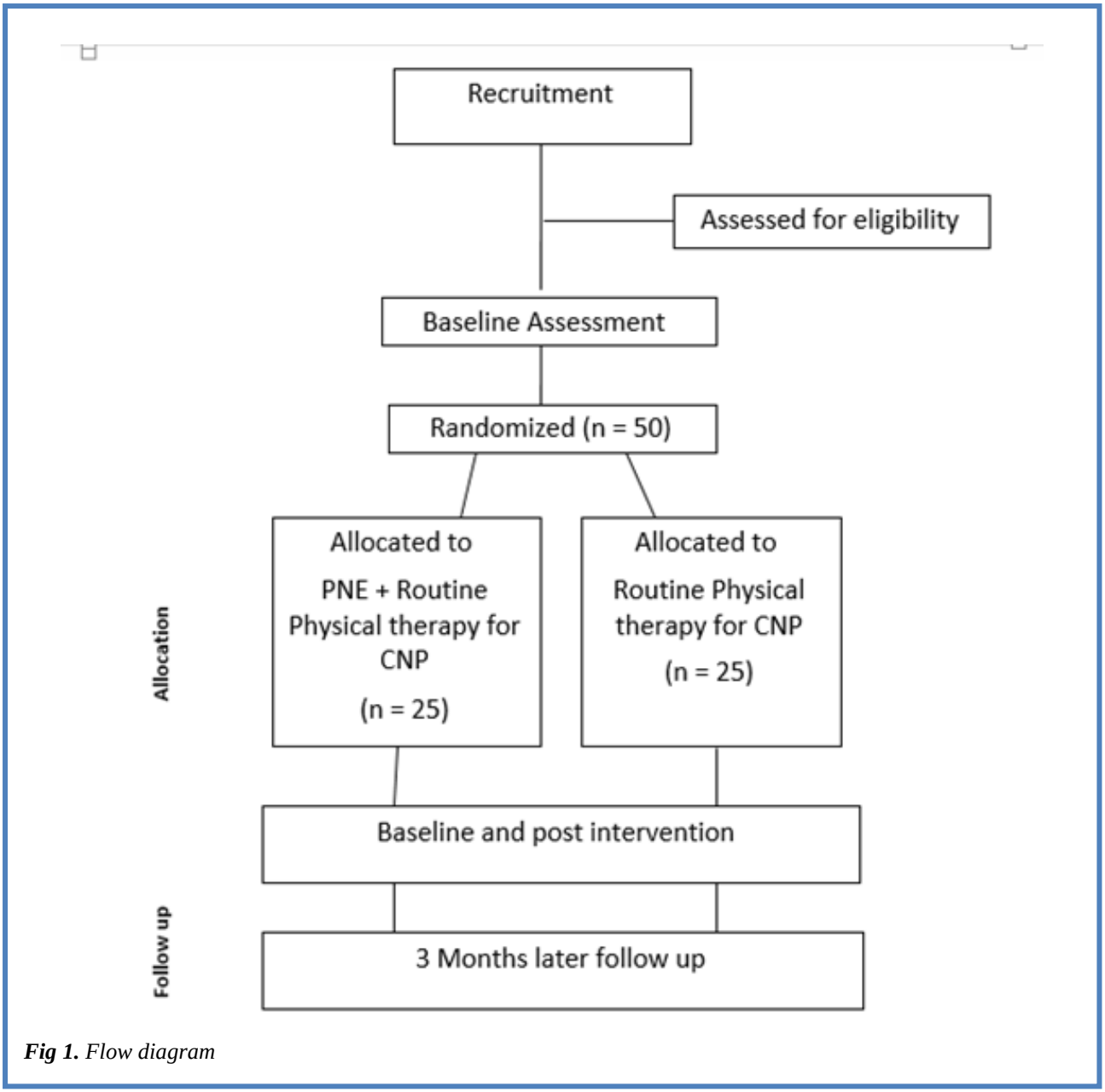


***Fig 1.*** *Flow diagram*

to gradually transit from static skills to dynamic and eventually functional skills.[17]

*Assessments and Blinding*

The outcome assessments will be performed by a physical therapist who is blinded toward treatment allocation. Additionally, patients will be blinded toward treatment groups.

*Outcomes*

Outcome measurements will be assessed in a random order at baseline, post interventions, and three months after the intervention (Figure 1 and Figure 2).

Visual Analogue Scale (VAS)

Neck pain intensity will be measured using a 100 mm visual analogue scale where 0 represented 'no pain' and 100 the 'worst pain imaginable'. Participants draw a mark at a point on the line that best reflects the pain they are experiencing at the time of measurement. Higher scores indicate higher pain levels.[18] The sensitivity and specificity of this questionnaire and the acceptability of its psychometric properties have been previously approved.[19,20]

Pressure Pain Threshold (PPT)

An algometer (LUTRON Force Gauge 5020, Taiwan) will be used to measure pressure pain thresholds at both the right and left upper trapezius (mid distance between the posterior angle of the acromion and C7), the web space and distal of quadriceps muscles (4 cm above patellar, in supine position).[21,22] The PPT on the upper trapezius will be measured with the patient comfortably

| | STUDY PERIOD | | | | |
|---|---|---|---|---|---|
| | **Enrolment** | **Allocation** | **Post-allocation** | | **Close-out** |
| **TIMEPOINT**** | **$-t_1$** | **0** | **$t_0$** | **$t_{post\ intervention}$** | **$t_{3\ Months}$** |
| **ENROLMENT:** | | | | | |
| **Eligibility screen** | X | | | | |
| **Informed consent** | X | | | | |
| **Allocation** | | X | | | |
| **INTERVENTIONS:** | | | | | |
| **[Pain Neuroscience Education + Routine Physiotherapy for Chronic Neck Pain]** | ← | → | | | |
| **[Routine Physiotherapy for Chronic Neck Pain]** | ← | → | | | |
| **ASSESSMENTS:** | | | | | |
| **[Visual Analogue Scale]** | | | X | X | X |
| **[Pressure Pain Threshold]** | | | X | X | X |
| **[Central Sensitization Inventory]** | | | X | X | X |
| **[Neck Disability Index]** | | | X | X | X |
| **[Pain Catastrophizing Scale]** | | | X | X | X |
| **[Tampa Scale of Kinesiophobia]** | | | X | X | X |
| **[Pain Vigilance and Awareness Questionnaire]** | | | X | X | X |
| **[Brief Illness Perception Questionnaire]** | | | X | X | X |
| **[Short Form Health Survey]** | | | X | X | X |

***Fig 2.*** *SPIRIT figure showing the schedule of enrollment, interventions, and assessments*

seated in an armless chair. Three measurements will be taken at each point.[23] A 30 second resting period will be allowed between measurements.[24] Measurement procedures are in line with previous studies. Pressure pain threshold measurements have good intra- (ICC=0.86) and inter rater (ICC=0.76) reliability.[25,26]

Central Sensitization Inventory (CSI)

The CSI questionnaire will be used for the assessment of the central sensitization in patients with CNP,27 which assesses the 25 chronic pain-related symptoms using a Likert scale. Where scoring one indicates that this symptom never occurs, and score five indicates that the targeted symptom always occurs. This questionnaire is routinely used to identify the related symptoms to central sensitivity and quantify them and provides acceptable reliability and dimensionality.[27-31]

The Neurophysiology of Pain Questionnaire

This questionnaire is used to assess patients' conceptualization of the biological mechanisms that underpin pain.[10,32,33] It has 19 questions and one point is allocated for each correctly answered question, up to a maximum of 19 points. The neurophysiology of pain

questionnaire has demonstrated good internal consistency (Cronbach α=0.91)

*Physical Performance-related Measures*

The neck disability index (NDI) questionnaire will be used for assessing the disability due to neck pain. It has excellent reliability and good convergent validity and responsiveness.[34,35]

*Psychosocial Measures*

Pain catastrophizing scale (PCS)

The 13-item Pain Catastrophizing Scale will be used to measure participants' tendency to magnify the threat value of a pain stimulus. The total score for this scale ranges from 0 to 52, with higher scores indicative of greater catastrophic thinking. The Persian version of the Pain Catastrophizing Scale is a reliable and valid instrument in measuring pain catastrophizing.[36,37]

Tampa Scale of kinesiophobia (TSK)

The Iranian version of the TSK will be used to evaluate kinesiophobia. This scale consists of 17 indices, each as a Likert 4 points measure ranging from totally disagrees to totally agree, which has been previously confirmed regarding validity and reliability.[38]

Pain Vigilance and Awareness Questionnaire (PVAQ)

The Persian version of the PVAQ will be used to assess patients' attention to pain. It is a 16-item criterion of pain attention that assesses awareness, alertness, vigilance, and pain observation. Scores range from 0 to 80, and high scores are related to over-care for pain.[39] The validity and reliability of Persian PVAQ has been evaluated by Nasrollahi et al. (2014).[40]

Brief Illness Perception Questionnaire (BIPQ)

The Brief IPQ is a nine-item scale designed to rapidly assess cognitive and emotional representations of the disease. The range of scores of the first 8 questions is from 1 to 10.
A higher score indicates a more threatening view of the disease, i.e., the person has a wrong perception of the disease. Question 9 The answer is open and examines the three main causes of the disease in order.
Evidence shows the Brief IPQ to be a valid and reliable measure of illness perceptions in a variety of illness groups.[41,42]
The Persian version of the BIPQ will be used to evaluate the five cognitive illness representations on a five-point Likert scale.[43]

Short Form Health Survey (SF36)

SF36 is a general health assessment tool that includes eight subscales: physical function, physical limitation, physical pain, general health, vitality, social functioning, mental health problems and mental health, which together constitute two measures: physical health summary and mental health summary. In addition, a question that examines changes in a person's health over a period of one year. These eight subscales are scored from 0 to 100, with higher scores indicating better health. The validated Iranian version of the SF-36 will be used to measure the health-related quality of life among the general population.[44,45]

Global perceived effect (GPE)

GPE rated on a 7-point scale (1 = completely recovered, 7 = worse than ever) to assess recovery. These ratings will be dichotomized into "improved" ("completely recovered" and "much improved") versus "not improved" ("slightly improved," "not changed," "slightly worsened," "much worsened," "worse than ever").

*Statistics*

The statistical analysis of the primary outcome measures will be performed according to an intention-to-treat analysis to handle non-adherence subjects. We will proceed with a repeated measures mixed model with patients as random effect and time (baseline, 1-2 days after treatment, and three months later) and treatment arm (PNE plus routine physical therapy or routine physical therapy alone) as fixed effects, and with adjustments for baseline imbalance. No imputation will take place.
Secondary outcomes and other endpoints will be analyzed similarly to the primary outcome.
The frequency of adverse events will be compared between groups at the 3-month follow-up using a Poisson regression model with robust error variance.
Categorical outcomes will be analyzed using a X2 test, Fisher exact test, or a Mann-Whitney U test as appropriate. A per-protocol analysis will be performed for the primary outcome, excluding patients who had poor adherence to the intervention, defined as participating in less than 75% of the exercise sessions and not attending both PNE sessions. A 95% confidence interval (CI) will be interpreted as a lack of a clinically meaningful difference between groups. P values and 95% CIs will be presented. All authors will have access to the final anonymized trial dataset.

*Trial Steering Committee*

The title page presents the members of the trial steering committee. All members participated in the conception of the study design and procured funding. The principal investigator (Kouhzad H) is coordinating the ongoing trial. The trial steering committee reviews the progress of the trial and agrees to the necessary changes in the protocol if any.

*Knowledge translation*

What is "already known" in this topic:
Limited studies have examined the effect of pain neuroscience education on the treatment of people with chronic neck pain.

*What this article adds*

In this study, the effect of pain neuroscience education will be investigated only on people with chronic neck pain with central sensitization involvement.

*Data Collection and Management*

All obtained results will be collected using a test score protocol or fulfilling questionnaires and, after that, entered into Excel (version 2016, Microsoft Corporation, Redmond, WA, USA). From Excel, data will be transferred into SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. All collected test score protocols and questionnaires will be kept in a locked place as backup. Access to study data is restricted only for investigators and anyone cannot be accessed without permission.

*Publication*

Results will be published regardless of the outcome. Authorship will be determined based on the guidelines from the International Committee of Medical Journal Editors. The authors do not have any publication restrictions.

## Discussion

This trial aims to investigate the effects of PNE combined with routine physical therapy compared to routine physical therapy alone in regard to psychological factors, physical performance, and the level of pain in patients with CNP. To the best of our knowledge, this is the first clinical trial conducted to evaluate the potential impact of PNE in this group of patients. This study will desire to determine whether the combination of PNE could regulate outcomes of patients with CNP.

This trial will be conducted using randomized allocation, double-blinded method, and clinically applicable interventions. The study interventions are conducted in clinical settings, thereby enhancing the possibility of future implementation of the treatments in the health care systems. These would be strengths of this trial.

On the limitation's aspects, it is noteworthy that the outcomes will be measured post intervention and 3 months after the interventions. Since the CNP is a chronic condition, longer follow-up periods would be beneficial to detect the impacts of interventions that could appear subsequently and also allows to compare the outcomes in various periods. Because patients in this study have chronic pain, the use of analgesics is unavoidable. In order to eliminate the effect of this possible confounder, it is better to pay attention to such cases in future studies.

## List of acronyms

BIPQ - Brief Illness Perception Questionnaire
CERT - Consensus on Exercise Reporting Template
CNP - chronic neck pain
GPE - Global perceived effect
NDI - neck disability index
PCS - Pain catastrophizing scale
PNE - pain neuroscience education
PVAQ - Pain Vigilance and Awareness Questionnaire
SF36 - Short Form Health Survey
SPIRIT - Standard Protocol Items: Recommendations for Interventional Trials
TIDieR - Template for Intervention Description and Replication
TSK - Tampa Scale of kinesiophobia

## Contributions of Authors

FS, HKM, MS, FD and GN participated in conception and design of the study, acquisition, analysis and interpretation of data, wrote the manuscript, performed literature review, article drafting and revision, reviewed and edited the manuscript critically, all authors have readed and approved the final editedversion.

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## Conflict of Interest

The authors declare no conflict of interests.

## Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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