Localized Pain Hypersensitivity in Older Women with Cervicogenic Headache: A Quantitative Sensory Testing Study

Jenjira Assapun, MSc
PhD Student
Department of Physical Therapy
Faculty of Associated Medical Sciences
Chiang Mai University
Chiang Mai, Thailand

Sureeporn Uthaikhup, PhD
Assistant Professor
Department of Physical Therapy
Faculty of Associated Medical Sciences
Chiang Mai University
Chiang Mai, Thailand
and Research Center in Back, Neck,
  Other Joint Pain and Human
  Performance (BNOJPH)
Khon Kaen University
Khon Kaen, Thailand

Correspondence to:
Dr Sureeporn Uthaikhup
Department of Physical Therapy
Faculty of Associated Medical Sciences
Chiang Mai University, Chiang Mai
  50200, Thailand
Fax: +66 5394 6042
Email: sureeporn.uthaikhup@cmu.ac.th

Aims: To investigate pain sensitivity by using quantitative sensory testing in older women with and without cervicogenic headache. **Methods:** A total of 18 older women (mean age ± standard deviation [SD] 64.28 ± 3.21 years) with cervicogenic headache and 17 healthy controls (65.18 ± 3.89 years) participated in the study. Pain thresholds (pressure, heat, and cold) and suprathreshold heat pain ratings (at 45°C, 47°C, and 49°C) were measured over the temporalis muscle, upper cervical spine, and tibialis anterior muscle. Analysis of variance was used to determine differences in pain outcomes between groups. **Results:** Compared to the control group, cold pain threshold in the cervicogenic headache patients was significantly decreased in the upper cervical region (P = .04) but not over the temporalis and tibialis anterior muscles (P > .05). There were no significant between-group differences in pressure pain threshold, heat pain threshold, or suprathreshold heat pain ratings at any sites (P > .05). **Conclusion:** Older women with cervicogenic headache have localized pain sensitivity to cold stimuli, suggesting peripheral mechanisms underlie the hyperalgesia. *J Oral Facial Pain Headache 2017;31:80–86. doi: 10.11607/ofph.1677*

Keywords: *cervicogenic headache, elderly, pain sensitivity, pain thresholds, suprathresholds*

Cervicogenic headache is a secondary headache caused by the upper cervical spine.[1] It has been suggested that cervicogenic headache is associated with cervical degenerative joint disease and becomes more frequent in older persons.[2,3] However, the mechanisms underlying cervicogenic headache in older persons remain unclear.

There has been a growing body of literature supporting the view that cervicogenic headache is a discrete headache that has pathophysiologic and pain mechanisms different from common migraine and tension-type headache.[4,5] Altered mechanical pain sensitivity has been identified over the occipital and upper cervical regions in patients with cervicogenic headache.[6–8] The altered mechanical pain sensitivity at a local site may reflect the presence of a peripheral nociceptive source.[9] Additionally, a recent study has demonstrated that patients with chronic cervical zygapophyseal joint pain with cervicogenic headache had cold and warm hyperalgesia on the painful side of the head and neck.[8] It has been suggested that rostral neuraxial spread of central sensitization might play a major role in the development of cervicogenic headache.[10–12]

Aging causes detrimental changes in the peripheral and central nervous systems. It can influence pain perception[13,14] and is also likely to influence the prevalence of pain and have clinical relevance to pain sensitivity in older persons with chronic pain.[15,16] There is extensive evidence of decreased pain sensitivity to pressure and thermal stimuli in older adults compared to younger persons,[14,17,18] although some reports indicate increased pain sensitivity.[19,20] Nevertheless, increased pain sensitivity is commonly experienced by older adults with chronic pain.[16] Also, pain perception in older adults can be complicated by the presence of comorbid conditions and psychological factors such as depression and anxiety.[21,22]

Cervicogenic headache has been proposed to be associated with cervical degenerative changes,[2,23] but little is known about pain sensitivity in older adults with cervicogenic headache. Uthaikhup et al[24] have investigated pain thresholds in older persons who suffer from chronic headache (migraine, tension-type headache, cervicogenic headache, and unclassifiable headache). Their results showed significantly decreased pain thresholds to heat stimuli, but not to pressure or cold stimuli, over the upper neck in elders with any type of headache compared to controls. Central sensitization was not found to be a feature of chronic headache in older persons. There is a need for further scientific evidence of pain thresholds in older persons with cervicogenic headache. A better understanding of pain perception would allow the adaptation of treatment for headache associated with neck pain that enhances the effectiveness of management in this age population.

Quantitative sensory testing (QST) is a valuable method to help assess underlying pain mechanisms.[25,26] The aim of this study was to investigate pain sensitivity by using QST (pain thresholds and suprathreshold responses) in older women with or without cervicogenic headache. As psychological factors and comorbid pain can influence pain thresholds,[21,22] these factors were considered as potential confounding variables. It is also evident that women have a lower pain threshold than men[27] and that the prevalence of cervicogenic headache is more frequent in women.[5] Therefore, only older women were included in the study.

Materials and Methods

Participants

The sample size used in this study was calculated based on cold pain thresholds (CPTs) over the cervical spine in a previous study.[28] A total sample size of approximately 28 (14 per group) was required to achieve a power of 80% with a significance level of .05 and an effect size of 1.[12]

A total of 35 older women, 18 cervicogenic headache patients and 17 healthy controls (both groups aged between 60 and 75 years), participated in the study. All participants were recruited through university and provincial hospitals as well as those advertising in the community. Participants with cervicogenic headache were diagnosed by a neurologist according to the Cervicogenic Headache International Study Group (CHISG).[29] The diagnostic criteria included unilateral dominant headache, pain starting in the neck, symptoms and signs of neck involvement, moderate, nonthrobbing, and nonlancinating pain, and pain episodes of varying duration. Participants

with cervicogenic headache had reported persistent intermittent headache at least once per month for the past year and were not considered if they reported two or more types of headache. The healthy controls had no previous history of neck pain and headache in the past 12 months. Participants were excluded if they had health conditions that could have an effect on outcome measures; ie, history of head and neck surgery, musculoskeletal disorders (eg, cervical radiculopathy, sciatica pain, and myopathy), neurologic problems (eg, Parkinson disease, stroke, and diabetes mellitus), and cognitive disturbance.

The study was approved by the institutional ethical review board and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from each participant prior to commencement of the study.

Questionnaires
General Questionnaire
A general questionnaire was developed to include demographic data, health status, medication use, and comorbid musculoskeletal pain (ie, shoulder, wrist, upper/lower back, hip, knee, and ankle/foot). The comorbid musculoskeletal pain was dichotomized as yes/no.

Neck Disability Index-Thai Version (NDI-TH)
The NDI-TH, consisting of 10 items, was used to assess levels of disability associated with neck pain. It was translated from its original version and has been shown to have good reliability.[30] Each item is scored from 0 (highest level of function) to 5 (lowest level of function), and the total score is expressed as a percentage.

Visual Analog Scale (VAS)
A 10-cm VAS was used to measure intensity of headache, where 0 indicated no pain and 10 the worst pain imaginable. The VAS has been shown to have good validity and reliability for assessing pain in older persons.[31]

Thai Geriatric Depression Scale-Long Form (TGDS-L)
The TGDS-L is a widely used self-report measure of depression in older persons. It consists of 30 items with yes/no answers, and a total score of ≥ 13 indicates depressive symptoms.[32] The TGDS-L was translated from the original version and has been shown to have high validity.[32]

QST
Pressure Pain Threshold (PPT)
PPT was assessed by using an electronic digital algometer with a 1-cm^2 circular probe (Somedic AB), according to the methods described elsewhere.[24,33] Pressure was applied at a constant rate of 40 kPa/s. The participant was instructed to press a button

when the sensation under the probe changed to pain. PPT was tested over the anterior part of the temporalis muscle (2 cm behind the lateral canthus of the eye and 2 cm above the orbital-meatal line) and the articular pillars of the cervical segment C2-C3. The areas tested are relevant to convergence of upper cervical and trigeminal sensory pathways through the trigeminocervical nucleus.[10–12,34] PPT was also tested over the upper one-third of the tibialis anterior muscle belly, a remote nonpainful site. PPT was measured bilaterally three times at each site with an interval of 30 seconds between each of the three times, and the mean values were used for analysis.

Intra- and interrater reliability of the PPT measurements were preliminarily conducted on 18 healthy individuals. The PPT measurements were performed on the right side of the temporalis muscle, the cervical spine (C2-3), and the tibialis anterior muscle. Participants were tested by the same investigator within a 48-hour interval for intrarater reliability and by two investigators within the same day for interrater reliability. The results showed excellent intrareliability (intraclass correlation coefficients [ICCs] ranged from 0.87 to 0.93) and interreliability (ICCs ranged from 0.81 to 0.93).

Thermal Pain Threshold (TPT)
Warm and cold pain thresholds were measured by using the TSA-II Neurosensory Analyzer (Medoc Ltd) with a 30 × 30-mm Peltier thermode, according to the methods described elsewhere.[24,33] The baseline temperature was set at 30°C with a thermal change rate of 1°C/second. To prevent tissue damage, the cut-off temperatures were set at 0°C and 50°C for CPTs and heat pain thresholds (HPTs), respectively. The participants were instructed to press a button when the thermal stimulus (cold or heat) first became painful. If the participants did not press the button prior to the cut-off temperature, the cut-off temperature was recorded for that trial. TPT was measured bilaterally over the anterior part of the temporalis muscle, the upper cervical region, and the upper one-third of the tibialis anterior muscle belly (a remote site). Each site was measured three times with 10-second intervals between each measurement, and the mean values were used for analysis.

Suprathreshold Heat Pain Ratings
Suprathreshold heat pain ratings were tested by using the TSA-II Neurosensory Analyzer (Medoc Ltd) with the 30 × 30-mm–diameter contact thermode. The baseline temperature was set at 35°C with a rate of increase of 4°C/second. The test consisted of three heat pulses (45°C, 47°C, and 49°C).[35] The pulses were applied in a random order and each pulse was kept constant for 5 seconds. A 10-second interval was used between measurements. The participants were instructed to rate the intensity of

pain for each pulse by using a 100-cm numeric rating scale (NRS), with 0 indicating no pain and 100 worst pain imaginable. Suprathreshold heat pain ratings were measured bilaterally over the anterior part of the temporalis muscle, the upper cervical region, and the upper one-third of the tibialis anterior muscle. Measurements were taken twice, and the mean values were used for analysis.

Procedure
Participants were asked to refrain from taking medication 24 hours prior to the day of testing. All participants completed the general and TGDS-L questionnaires. Participants with headache also completed the NDI-TH and VAS questionnaires. The QST was performed in a quiet and temperature-controlled room (24 ± 1°C). A familiarization trial was first given over the medial side of the forearm. The QST measures were then performed in a standard order: PPT, HPT, CPT, and suprathreshold heat pain rating. PPT over the upper cervical region was measured with the participant in a prone position, and PPT over the temporalis and tibialis anterior muscles with the participant in a supine position. To test TPT and suprathreshold heat pain ratings at all sites, participants were asked to sit on a chair with their feet resting on the floor or a footstool. The testing sites were randomly tested by an assessor blinded to the participant's condition.

Statistical Analyses
Paired *t* test analyses were preliminarily used to determine differences between sides for pain thresholds and suprathreshold heat pain ratings. No differences between side-to-side values were found for both groups ($P > .05$). The mean values of the left and right sides were then used for between-group comparisons. Univariate analyses of covariance were used to determine differences for PPTs and TPTs, and mixed model analysis of variance (ANOVA) for suprathreshold heat pain ratings between the headache and control groups. Differences in demographic data between groups were initially tested by using independent *t* test and chi-square test. A significant difference was evident in comorbid musculoskeletal pain between the groups. Comorbid musculoskeletal pain was then entered as a covariate in the univariate analyses of covariance and mixed model ANOVA. Preliminary analyses revealed no effects of headache on the examination day on pain measures ($P > .05$). Pearson correlations were used to identify associations between pain thresholds and TGDS-L scores. Statistical analyses were performed by using SPSS statistical package (version 17), and the significance level was set at $P < .05$.

Results

Participant Characteristics

The demographic characteristics of the headache and control groups are presented in Table 1. There were no significant differences between the two groups for age and TGDS-L scores ($P > .05$). The TGDS-L scores for both groups were low (< 13/30). The headache group had greater comorbid musculoskeletal pain (wrist, shoulder, back, and knee) than controls ($P < .01$). Nine participants in the headache group reported that they took medications to relieve their headaches (seven with paracetamol 500 mg, one with ibuprofen 200 mg + paracetamol 500 mg, one with paracetamol 500 mg + orphenadrine citrate 35 mg) and refrained from taking medications during the 24-hour period before testing.

None of the control participants had received pain or antidepressant medications in the past 12 months.

Pain Thresholds

Table 2 presents the results of PPT and TPT of the headache and control groups. Participants with cervicogenic headache had significantly decreased CPT over the cervical spine compared to controls after controlling for comorbid musculoskeletal pain ($P < .05$, $\eta^2 p = 0.13$). There were no significant differences between the two groups in PPT and HPT at any sites nor in CPT over the temporalis and tibialis anterior muscles ($P > .05$, $\eta^2 p$ ranged from 0.001 to 0.10).

An analysis investigating PPT and TPT between the cervicogenic headache group (n = 18) and the control group without the five control participants who had comorbid musculoskeletal pain (n = 12) revealed similar results to those noted before.

Suprathreshold Heat Pain Ratings

There were no significant differences between the headache and control groups for suprathreshold heat pain rating (45°C, 47°C, 49°C) at any sites after controlling for TGDS-L scores and comorbid pain ($P > .05$). No interaction effects between group and suprathreshold heat pain ratings were found ($P > .05$) (Table 3).

Correlations Between Pain Thresholds and TGDS-L

There were no significant correlations between any of the pain thresholds and TGDS-L scores (r ranged from 0.02 to 0.25; $P > .05$).

Table 1 Baseline Characteristics of Participants

Variables	CEH patients (n = 18)	Controls (n = 17)	P value
Age (y)	64.3 ± 3.2	65.2 ± 3.9	.46[a]
Headache intensity (VAS)	5.3 ± 1.6	–	
Headache history (y)	3.6 ± 2.9	–	
Headache frequency (d/wk)	3.3 ± 2.0	–	
NDI	25.1 ± 9.1	–	
TGDS-L	5.7 ± 4.3	4.6 ± 2.6	.35[a]
Headache on testing day (y/n)	8	–	
Medication use	9	0	< .01[b]
Comorbid musculoskeletal pain (y/n)	16	5	< .01[b]
Wrist pain	1	0	
Shoulder pain	7	1	
Back pain	2	1	
Knee pain	6	3	

Data are mean ± SD unless otherwise indicated. CEH = cervicogenic headache; VAS = visual analog scale (1–10 cm); NDI = Neck Disability Index (0–100 points); TGDS-L = Thai Geriatric Depression Scale-Long Form (0–30 points). [a]Differences between groups were tested using independent t test and [b]chi-square test.

Table 2 Pressure and Thermal Pain Thresholds of the Headache and Control Groups

Variables	CEH patients (n = 18)	Controls (n = 17)	P value[a]
PPT (kPa)			
Temporalis	154.1 ± 42.9	177.1 ± 57.0	.58
Upper cervical spine	191.5 ± 56.8	209.8 ± 70.1	.81
Tibialis anterior	264.9 ± 54.6	338.4 ± 106.8	.07
HPT (°C)			
Temporalis	40.1 ± 4.2	41.9 ± 3.2	.83
Upper cervical spine	42.1 ± 3.3	44.6 ± 4.2	.11
Tibialis anterior	44.5 ± 3.5	45.4 ± 2.3	.27
CPT (°C)			
Temporalis	13.8 ± 7.7	11.4 ± 6.8	.31
Upper cervical spine	9.5 ± 7.3	4.4 ± 5.2	.04
Tibialis anterior	8.8 ± 8.3	7.0 ± 6.5	.27

Data are mean ± SD unless otherwise indicated. CEH = cervicogenic headache; PPT = pressure pain threshold; HPT = heat pain threshold; CPT = cold pain threshold. [a]Differences between groups were tested using univariate analysis of covariance, controlling for comorbid musculoskeletal pain.

Table 3 Suprathreshold Heat Pain Ratings of the Headache and Control Groups

Site	Suprathreshold heat pain ratings (0–100 NRS)			P value[a]
	At 45°C	At 47°C	At 49°C	
Temporalis				
CEH (n = 18)	41.9 ± 24.2	51.4 ± 24.8	74.2 ± 24.5	.47
Control (n = 17)	41.7 ± 21.4	54.9 ± 21.7	70.6 ± 24.5	
Upper cervical spine				
CEH (n = 18)	43.9 ± 23.2	55.1 ± 25.3	63.9 ± 29.2	.83
Control (n = 17)	41.9 ± 24.7	53.8 ± 25.5	61.2 ± 26.5	
Tibialis anterior				
CEH (n = 18)	37.1 ± 25.2	46.3 ± 25.6	74.0 ± 24.8	.50
Control (n = 17)	35.5 ± 21.4	50.9 ± 21.9	69.8 ± 27.8	

Data are mean ± SD unless otherwise noted. CEH = cervicogenic headache; NRS = numeric rating scale. [a]Differences between groups were tested using mixed model ANOVA, controlling for comorbid musculoskeletal pain.

Discussion

This study has demonstrated that older women with cervicogenic headache had decreased pain thresholds to cold stimuli at the upper cervical region, but not over the temporalis and tibialis anterior muscles. There were no differences in pressure and heat pain sensitivity nor in the pain ratings to heat stimuli at any site between older persons with and without cervicogenic headache. The results of this study support the view that cervicogenic pain may be maintained or modulated by peripheral nociceptive inputs and suggest that the pain sensitivity response may depend on the types of nociceptive stimuli.

Cervicogenic headache is a syndrome in which pain originates from structures innervated by the cervical nerve root C1-3.[1] The lower CPT over the cervical region may be interpreted as indicating the source of pain. The results of this study are in agreement with available evidence in general populations that suggests an increase occurs in pain sensitivity over the upper cervical nerve roots and joints in cervical headache.[6,7,24,36] The increased pain sensitivity could reflect peripheral sensitization of the peripheral afferent nerve fibers.[9] The mechanism of cervicogenic headache likely involves the trigeminocervical nucleus, which receives nociceptive afferent inputs from the cervical structures.[10–12,34] Nevertheless, although peripheral sensitization in cervicogenic headache may appear to be consistent among studies, reduced pain thresholds and increased responsiveness of nociceptors may be attributed to several factors including the type of noxious stimulus.[37] It has been suggested that nociceptive pathways are specific and subject to complex facilitating and inhibitory control.[38] While the present study found lower pain thresholds to cold stimuli over the cervical spine in older adults with cervicogenic headache, another study[24] has reported lower pain thresholds to heat stimuli, but only a nonsignificant trend toward a decrease in the mean HPT was found in this study. The discrepancy between the results of this study and the earlier study may be related to characteristics of the control subjects. Notably, the mean values for HPT and CPT in the control group in this study were relatively lower or higher than those in the earlier study, but there were no significant differences in pain thresholds in cervicogenic headache subjects between the two studies. A factor of comorbid musculoskeletal pain was not included in the earlier study. Alternatively, no decreased pain sensitivity to mechanical (pressure) stimuli was observed in either this study or the earlier study. Decreased pain thresholds to thermal stimuli in older adults with cervicogenic headache may be associated with age-related changes in the nervous system. There is evidence for more pronounced alterations in myelinated (A-delta) nerve fibers than in unmyelinated (C) nerve fibers with increasing age.[39] The A-delta fiber system is involved in the mediation of cold and pressure sensation, and together with C fibers, transmission of signals related to nociceptive cold, heat, and pressure pain stimuli. Any alteration in A-delta nerve activity might conceivably cause disinhibition of C-fiber activity, resulting in an increased pain sensitivity.

A reduction in pain sensitivity at remote sites and increased responses to suprathreshold stimulation are suggestive of augmented central nociceptive processing, which is also known as central sensitization.[38] It is known that ongoing peripheral input has an influence on altered central pain processing and descending pain modulation.[12,40,41] However, the peripheral noxious stimulus must be intense, repeated, and sustained.[38] In this study, the presence of generalized pain sensitivity detected by QST (pain thresholds and suprathreshold heat pain ratings) was not found in older adults with cervicogenic headache, which is consistent with previous findings.[24,42] The findings from the previous and present studies support the view that central sensitization may not be a feature of older adults with cervicogenic headache. Additionally, several studies have indicated that psychological factors influence pain sensitivity and may play a role in the development or maintenance of chronic pain conditions.[20,43] However, in this study, pain thresholds were independent of level of depression scores. The older adults with headache had scores < 13/30 on the TGDS-L; these values are considered relatively normal. The results of this study are in line with previous findings demonstrating that depressive symptoms did not appear to influence pain thresholds in older adults with cervicogenic headache.[24] It is possible that older persons with cervicogenic headache have learned to adapt or get used to the pain.

There were some limitations in this study that need to be addressed. Sample size of this study was relatively small. The statistical power levels of the nonsignificant results were less than 0.8, indicating inadequate power to detect statistical significance. Evidence suggests that musculoskeletal pain is common in older adults[44]; thus, it was difficult to recruit older adults who have only cervicogenic headache and healthy older adults without musculoskeletal pain. The experience of musculoskeletal pain may influence pain sensitivity. However, in this study, the presence of musculoskeletal pain was taken into account when considering pain sensitivity between the two groups. Additionally, the chronic use of opioids may influence pain sensitivity, although a study demonstrated that chronic opioid intake might reduce the temperature sensitivity but not pain sensitivity measured by QST.[45] Nonetheless, the present study has provided

evidence for the clinical relevance of localized cold pain sensitivity in older adults with cervicogenic headache. Thermal modalities should be used with caution over the cervical region in older adults with cervicogenic headache. It has been increasingly recognized that reduced conditioned pain modulation reflects impairment in pain inhibitory mechanisms associated with chronic pain syndromes.[46] Further research should include conditioned pain modulation to test endogenous inhibitory pain pathways in older adults with cervicogenic headache.

Conclusions

This study has demonstrated localized pain sensitivity over the upper cervical region in older women with cervicogenic headache. There were no significant differences in pressure and heat pain sensitivity and the pain ratings to heat stimuli at any sites between older persons with and without cervicogenic headache.

Acknowledgments

References

1. Bogduk N. The neck and headaches. Neurol Clin 2004;22: 151–171.
2. Pearce JM. The importance of cervicogenic headache in the over-fifties. Headache Q, Curr Treatment Res 1995;6:293–296.
3. Lang JK, Buchfelder M. Radiofrequency neurotomy for headache stemming from the zygapophysial joints C2/3 and C3/4. Cent Eur Neurosurg 2010;71:75–79.
4. Bartsch T, Goadsby PJ. Anatomy and physiology of pain referral patterns in primary and cervicogenic headache disorders. Headache Curr 2005;2:42–48.
5. Sjaastad O. Cervicogenic headache: Comparison with migraine without aura; Vågå study. Cephalalgia 2008;28(suppl):18–20.
6. Bovim G. Cervicogenic headache, migraine, and tension-type headache: Pressure-pain threshold measurements. Pain 1992;51:169–173.
7. Zito G, Jull G, Story I. Clinical tests of musculoskeletal dysfunction in the diagnosis of cervicogenic headache. Man Ther 2006;11:118–129.
8. Chua NH, van Suijlekom HA, Vissers KC, Arendt-Nielsen L, Wilder-Smith OH. Differences in sensory processing between chronic cervical zygapophysial joint pain patients with and without cervicogenic headache. Cephalalgia 2011;31:953–963.
9. Koltzenburg M. Neural mechanisms of cutaneous nociceptive pain. Clin J Pain 2000;16(suppl):S131–S138.
10. Mørch CD, Hu JW, Arendt-Nielsen L, Sessle BJ. Convergence of cutaneous, musculoskeletal, dural and visceral afferents onto nociceptive neurons in the first cervical dorsal horn. Eur J Neurosci 2007;26:142–154.
11. Sessle BJ, Hu JW, Amano N, Zhong G. Convergence of cutaneous, tooth pulp, visceral, neck and muscle afferents onto nociceptive and non-nociceptive neurones in trigeminal subnucleus caudalis (medullary dorsal horn) and its implications for referred pain. Pain 1986;27:219–235.
12. Vernon H, Sun K, Zhang Y, Yu XM, Sessle BJ. Central sensitization induced in trigeminal and upper cervical dorsal horn neurons by noxious stimulation of deep cervical paraspinal tissues in rats with minimal surgical trauma. J Manipulative Physiol Ther 2009;32:506–514.
13. Cole LJ, Farrell MJ, Gibson SJ, Egan GF. Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. Neurobiol Aging 2010;31:494–503.
14. Lautenbacher S. Experimental approaches in the study of pain in the elderly. Pain Med 2012;13(suppl):S44–S50.
15. Thomas E, Mottram S, Peat G, Wilkie R, Croft P. The effect of age on the onset of pain interference in a general population of older adults: Prospective findings from the North Staffordshire Osteoarthritis Project (NorStOP). Pain 2007;129:21–27.
16. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23: 1043–1056.
17. Riley JL 3rd, Cruz-Almeida Y, Glover TL, et al. Age and race effects on pain sensitivity and modulation among middle-aged and older adults. J Pain 2014;15:272–282.
18. Marini I, Bortolotti F, Bartolucci ML, Inelmen EM, Gatto MR, Bonetti GA. Aging effect on pressure pain thresholds of head and neck muscles. Aging Clin Exp Res 2012;24:239-244.
19. Pickering G, Jourdan D, Eschalier A, Dubray C. Impact of age, gender and cognitive functioning on pain perception. Gerontology 2002;48:112–118.
20. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 2005;115:410–418.
21. Kose N, Ekici G, Karakaya MG, Suvalci S, Demir B, Otman AS. The assessment of the pressure pain threshold and its correlation with depression and anxiety in geriatric nursing home residents with cognitive impairment. Pain Clin 2004;16:201–206.
22. Leong IY, Farrell MJ, Helme RD, Gibson SJ. The relationship between medical comorbidity and self-rated pain, mood disturbance, and function in older people with chronic pain. J Gerontol A Biol Sci Med Sci 2007;62:550–555.
23. Lang JK, Buchfelder M. Radiofrequency neurotomy for headache stemming from the zygapophysial joints C2/3 and C3/4. Cent Eur Neurosurg 2010;71:75–79.
24. Uthaikhup S, Sterling M, Jull G. Widespread sensory hypersensitivity is not a feature of chronic headache in elders. Clin J Pain 2009;25:699–704.
25. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556–572.
26. Pavlakovic G, Petzke F. The role of quantitative sensory testing in the evaluation of musculoskeletal pain conditions. Curr Rheumatol Rep 2010;12:455–461.
27. Bartley EJ, Fillingim RB. Sex differences in pain: A brief review of clinical and experimental findings. Br J Anaesth 2013; 111:52–58.
28. Javanshir K, Ortega-Santiago R, Mohseni-Bandpei MA, Miangolarra-Page JC, Fernandez-de-Las-Peñas C. Exploration of somatosensory impairments in subjects with mechanical idiopathic neck pain: A preliminary study. J Manipulative Physiol Ther 2010;33:493–499.

29. Sjaastad O, Fredriksen TA, Pfaffenrath V. Cervicogenic headache: Diagnostic criteria. The Cervicogenic Headache International Study Group. Headache 1998;38:442–445.

30. Uthaikhup S, Paungmali A, Pirunsan U. Validation of Thai versions of the Neck Disability Index and Neck Pain and Disability Scale in patients with neck pain. Spine (Phila Pa 1976) 2011; 36:E1415–E1421.

31. Tiplady B, Jackson SH, Maskrey VM, Swift CG. Validity and sensitivity of visual analogue scales in young and older healthy subjects. Age Ageing 1998;27:63–66.

32. Train the Brain Forum Committee. Thai Geriatric. Depression Scale-TGDS. Siriraj Hosp Gaz 1994;46:1–9.

33. Scott D, Jull G, Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. Clin J Pain 2005;21:175–181.

34. Bartsch T, Goadsby PJ. The trigeminocervical complex and migraine: Current concepts and synthesis. Curr Pain Headache Rep 2003;7:371–376.

35. Harkins SW, Price DD, Martelli M. Effects of age on pain perception: Thermonociception. J Gerontol 1986;41:58–63.

36. Anthony M. Cervicogenic headache: Prevalence and response to local steroid therapy. Clin Exp Rheumatol 2000;18:S59–S64.

37. Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin J Pain 2004;20:227–239.

38. Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. J Pain 2009; 10:895–926.

39. Kemp J, Després O, Pebayle T, Dufour A. Differences in age-related effects on myelinated and unmyelinated peripheral fibres: A sensitivity and evoked potentials study. Eur J Pain 2014; 18:482–488.

40. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. Ann Neurol 2013;74:630–636.

41. Kobayashi A, Shinoda M, Sessle BJ, et al. Mechanisms involved in extraterritorial facial pain following cervical spinal nerve injury in rats. Mol Pain 2011;7:12.

42. Svensson P, Wang K, Arendt-Nielsen L, Cairns BE, Sessle BJ. Pain effects of glutamate injections into human jaw or neck muscles. J Orofac Pain 2005;19:109–118.

43. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine (Phila Pa 1976) 2002;27:E109–E120.

44. Buchman AS, Shah RC, Leurgans SE, Boyle PA, Wilson RS, Bennett DA. Musculoskeletal pain and incident disability in community-dwelling older adults. Arthritis Care Res (Hoboken) 2010;62:1287–1293.

45. Wang H, Fischer C, Chen G, Weinsheimer N, Gantz S, Schiltenwolf M. Does long-term opioid therapy reduce pain sensitivity of patients with chronic low back pain? Evidence from quantitative sensory testing. Pain Physician 2012;15: ES135–ES143.

46. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 2015;156(suppl):S24–S31.