CHAPTER 4

Study II: Localized pain hypersensitivity in older women with cervicogenic headache: A quantitative sensory testing study

4.1 Introduction

Cervicogenic headache is a secondary headache caused by the upper cervical spine (103). It is suggested that cervicogenic headache is associated with cervical degenerative joint disease and becomes more frequent in older persons (26, 27). However, an understanding of pain mechanisms of cervicogenic headache in older persons remains unclear.

There has been a growing body of literature providing that cervicogenic headache is a discrete headache which has different pathophysiologic and pain mechanisms from common migraine and tension-type headache (189, 190). Altered mechanical pain sensitivity has been identified over the occipital and upper cervical regions in patients with cervicogenic headache (110, 145, 146). The altered mechanical pain sensitivity at a local site reflects the presence of a peripheral nociceptive source (191). 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 (146). It was suggested that rostral neuraxial spread of central sensitization might play a major role in the development of cervicogenic headache (192-194).

Aging causes detrimental changes in the peripheral and central nervous system. It manifests pain perception (64, 65) and is likely to influence prevalence of pain and clinical relevance of pain sensitivity in older persons with chronic pain (195, 196). There is an extensive evidence of a decreased pain sensitivity for pressure and thermal stimuli in older adults compared to younger persons (65, 78, 197), although some reports indicates increased pain sensitivity (198, 199). Nevertheless, increased pain sensitivity is commonly experienced by older adults with chronic pain (196). Also, pain perception in older adults can be complicated by the presence of comorbid conditions and psychological factors such as depression and anxiety (200, 201).

Whereas cervicogenic headache has been proposed to be associated with cervical degenerative changes (26, 27), little is known about pain sensitivity in older adults with cervicogenic headache. Uthaikhup et al (11) have investigated pain thresholds in elders who suffered from chronic headache (migraine, tension-type headache, cervicogenic headache and unclassifiable headache). The results showed decreased pain thresholds to heat stimuli over the upper neck but not to pressure and cold stimuli in elders with any type of headache compared to controls. Central sensitization was not found to be a feature of chronic headache in elders. There is a need for further scientific evidence of pain thresholds in older adults 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 assess the underlying pain mechanism (133, 202). Thus the aim of this study was to investigate pain sensitivity in older adults with and without cervicogenic headache using QST (pain thresholds and supra-threshold responses). As psychological factors and comorbid pain can influence pain thresholds (200, 201), these factors were considered as potential confounding variables. It is also evident that women have a lower pain threshold than men (203) and the prevalence of cervicogenic headache is more frequent in women (190). Therefore only older women were included in the study.

4.2 Methods

4.2.1 Sample size calculation

The sample size used in this study was calculated based on cold pain thresholds over the cervical spine in the previous study (204). The total sample size of approximately 28 (14 per group) was required to achieve a power of 80% with a significance level of 0.05 and an effect size of 1.12.

4.2.2 Participants

Thirty-five older women including 18 cervicogenic headache and 17 healthy controls, aged between 60-75 years, participated in the study. All participants were recruited through a 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) (105). The diagnostic criteria included unilateral dominant headache, pain starting in the neck, symptoms and signs of neck involvement, moderate, non-throbbing and non-lancinating pain, and pain episodes of varying duration. Participants with cervicogenic headache had reportedly 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. 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 i.e. history of head and neck surgery, musculoskeletal disorders (e.g. cervical radiculopathy, sciatica pain and myopathy), neurological problems (e.g. Parkinson's 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.

4.2.3 Questionnaires

4.2.3.1 Questionnaires

Questionnaires included the general questionnaire (demographic data, medical condition and comorbid musculoskeletal pain (i.e. shoulder, wrist, upper/lower back, hip, knee and ankle/foot)), headache questionnaire, NDI-TH, VAS and Thai Geriatric Depression Scale-Long Form (TGDS-L). Details of all questionnaires except for the TGDS-L are provided in Sections 3.2.3.1-3.2.3.4 and Appendices A-D.

4.2.3.2 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 a 30 items with yes/no answers and a total score of ≥ 13 indicates depressive symptoms (205). The TGDS-L was translated from the original version and shown to have high validity (205). Details of this questionnaire are provided in Appendix E.

4.2.4 Quantitative Sensory Testing

4.2.4.1 Pressure pain thresholds (PPTs)

PPTs were assessed using an electronic digital algometer with a 1 cm^2 circular probe (Somedic AB, Sollentuna, Sweden) according to the methods described elsewhere (11, 206). 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. PPTs were 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 (Figure 4.1). The areas tested are relevant to convergence of upper cervical and trigeminal sensory pathways through the trigeminocervical nucleus (88, 192-194). PPTs were also tested over the upper one third of the tibialis anterior muscle belly, a remote non-painful site. PPTs were measured bilaterally three times at each site, with an interval of 30 seconds and the mean values were used for analysis.

Intra- and inter-rater reliability of the PPT measurements was preliminarily conducted on 18 healthy individuals. The PPT measurements were performed on the right side at the temporalis muscle, the cervical spine (C2-3) and the tibialis anterior muscle. Participants were measured by the same investigator within a 48-hour interval for intra-rater reliability and by two investigators within the same day for inter-rater reliability. The results showed excellent intra-reliability (intraclass correlation coefficients (ICCs) ranged from 0.87 to 0.93) and inter-reliability (ICCs ranged from 0.81 to 0.93). Details of reliability are provided in Appendices I and J.

Figure 4.1 Pressure pain thresholds at the upper cervical region

4.2.4.2 Thermal pain thresholds (TPTs)

Warm and cold pain thresholds were measured using the TSA-II Neurosensory Analyzer (Medoc Ltd; Ramat Yishai, Israel) with a 30 x 30 mm Peltier thermode according to the methods described elsewhere (11, 206). The baseline temperature was set at 30 °C with a thermal rate change of 1 °C/s. To prevent tissue damage, the cut-off temperature was set at 0 °C and 50 °C for cold pain thresholds (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. TPTs 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 belly (a remote site) (Figure 4.2). Each site was measured three times with 10 second intervals between each trial and the mean values were used for analysis.

4.2.4.3 Supra-threshold heat pain ratings

Supra-threshold heat pain rating was tested using the TSA-II Neurosensory Analyzer (Medoc Ltd; Ramat Yishai, Israel) with the 30 x 30 mm diameter contact thermode. The baseline temperature was set at 35 °C with a rate of increase 4 °C/s. The test consisted of three heat pulses (45 °C, 47 °C and 49 °C) (81). Each pulse was applied in random order and was kept constant for five seconds. A 10-

second interval was used between trials. The participants were instructed to rate the intensity of pain for each pulse using a numerical rating scale (NRS) (0 = no pain and 100 = worst pain imaginable). Supra-threshold 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 (Figure 4.2). Measures were taken twice and the mean values were used for analysis.

Figure 4.2 Thermal pain threshold and supra-threshold heat pain rating at tibialis anterior muscle

4.2.5 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 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: PPTs, HPTs, CPTs and supra-threshold heat pain ratings. PPTs over the upper cervical region were measured with participants in a prone position and PPTs over the temporalis and tibialis anterior muscles in a supine position. To test TPTs and supra-threshold heat pain ratings in 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.

4.2.6 Statistical analysis

Paired t-test analyses were preliminary used to determine differences between sides for pain thresholds and supra-threshold heat pain ratings. No differences between side to side were found for both groups ($p > 0.05$). 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 ANOVA for supra-threshold heat pain ratings between the headache and control groups. Differences in demographic data between groups were initially tested using Independent t-test and Chi-square. 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 ($p > 0.05$). Pearson correlations were used to identify associations between pain thresholds and TGDS-L scores. Statistical analyses were performed using SPSS statistical package (version 17) and significance level was set at $p < 0.05$.

4.3 Results

4.3.1 Participant characteristics

The demographic characteristics of the headache and control groups are presented in Table 4.1. There were no significant differences between the two groups for age and TGDS-L scores ($p > 0.05$). 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 ($p < 0.05$). Nine participants in the headache group reported that they took medications to relieve their headaches (7 with paracetamol 500 mg, 1 with ibuprofen 200 mg + paracetamol 500 mg, 1 with paracetamol 500 mg + orphenadrine citrate 35 mg), and refrained from taking medications during a 24 hour period before testing. None of controls received pain and antidepressant medications in the past 12 months.

4.3.2 Pain thresholds

Table 4.2 presents the results of PPTs and TPTs between the headache and control groups. Participants with cervicogenic headache had decreased CPT over the cervical spine compared to controls after controlling for comorbid musculoskeletal pain ($p < 0.05$, $\eta^2p = 0.13$). There were no significant differences between the two groups in PPTs and HPTs at any sites and CPTs over the temporalis and tibialis anterior muscles ($p > 0.05$, η^2p ranged from 0.001 to 0.10).

The analysis investigating differences in PPTs and TPTs between the cervicogenic headache group (n = 18) and the control group without five participants with comorbid musculoskeletal pain (n = 12) revealed similar results.

4.3.3 Supra-threshold heat pain ratings

There were no significant differences between the headache and control groups for supra-threshold heat pain ratings (45 °C, 47 °C, 49 °C) at any sites after controlling for comorbid musculoskeletal pain ($p > 0.05$). No interaction effects between group and supra-threshold heat pain ratings were found ($p > 0.05$) (Table 4.3).

4.3.4 Correlations between pain thresholds and TGDS-L

There were no significant correlations between pain thresholds (pressure, heat and cold) and TGDS-L scores (r ranged from 0.02 to 0.25; $p > 0.05$).

Table 4.1 Baseline characteristics of participants

Variables	CEH (n = 18)	Control (n = 17)	p-value
Age (yrs)	64.3 ± 3.2	65.2 ± 3.9	0.46[a]
Headache intensity (VAS, 1-10)	5.3 ± 1.6	-	
Headache history (yrs)	3.6 ± 2.9	-	
Headache frequency (days/week)	3.3 ± 2.0	-	
NDI (0-100)	25.1 ± 9.1	-	
TGDS-L (0-30)	5.7 ± 4.3	4.6 ± 2.6	0.35[a]
Headache on testing day (yes, n)	8	-	
Medication use	9	0	< 0.01[b]
Comorbid musculoskeletal pain (yes, n)	16	5	< 0.01[b]
Wrist pain	1	0	
Shoulder pain	7	1	
Back pain	2	1	
Knee pain	6	3	

Data are mean ± SD unless otherwise indicated.

[a] Differences between groups were tested using independent t-test, [b] using chi-square test

CEH, cervicogenic headache; VAS, visual analog scale; NDI, neck disability index; TGDS-L, Thai geriatric depression scale-long form

Table 4.2 Pressure and thermal pain thresholds between the headache and control groups

Variables	CEH (n = 18)	Control (n = 17)	*p*-value[a]
PPTs (kPa)			
Temporalis	154.1 ± 42.9	177.1 ± 57.0	0.58
Upper cervical spine	191.5 ± 56.8	209.8 ± 70.1	0.81
Tibialis anterior	264.9 ± 54.6	338.4 ± 106.8	0.07
HPTs (°C)			
Temporalis	40.1 ± 4.2	41.9 ± 3.2	0.83
Upper cervical spine	42.1 ± 3.3	44.6 ± 4.2	0.11
Tibialis anterior	44.5 ± 3.5	45.4 ± 2.3	0.27
CPTs (°C)			
Temporalis	13.8 ± 7.7	11.4 ± 6.8	0.31
Upper cervical spine	9.5 ± 7.3	4.4 ± 5.2	**0.04**
Tibialis anterior	8.8 ± 8.3	7.0 ± 6.5	0.27

Data are mean ± SD.

[a] Differences between groups were tested using univariate analysis of covariance, controlling for comorbid musculoskeletal pain

CEH, cervicogenic headache; PPTs, pressure pain thresholds; HPTs, heat pain thresholds; CPTs, cold pain thresholds

Table 4.3 Supra-threshold heat pain ratings between the headache and control groups

Site	Group	Supra-threshold heat 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	0.47
	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	0.83
	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	0.50
	Control (n = 17)	35.5 ± 21.4	50.9 ± 21.9	69.8 ± 27.8	

Data are mean ± SD.

[a] Differences between groups were tested using mixed model ANCOVA, controlling for comorbid musculoskeletal pain

CEH, cervicogenic headache; NRS, numerical rating scale

4.4 Discussion

The study demonstrated that older persons 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, and the pain ratings to heat stimuli at any sites between older persons with and without cervicogenic headache. The results of this study support that cervicogenic pain is maintained or modulated by the peripheral nociceptive input, and suggest that the pain sensitivity response may depend on types of nociceptive stimuli.

Cervicogenic headache is a syndrome that pain originates from structures innervated by the cervical nerve root C1-3 (103). Lower cold pain threshold 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 suggesting increase in pain sensitivity over the upper cervical nerve roots and joints in cervical headache (145, 147). The increased pain sensitivity of the peripheral nerve fibers could reflect peripheral sensitization (191). The mechanism of cervicogenic headache is likely to be restricted to the trigemino-cervical region which receives nociceptive afferent input from the cervical structures. 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 types of noxious stimulus (76). It has been suggested that nociceptive pain pathways are specific and subject to complex facilitating and inhibitory control (207). Whereas we found lower pain thresholds to cold stimuli over the cervical spine in older adults with cervicogenic headache, the results of Uthaikhup et al's study (11) demonstrated lower pain thresholds to heat stimuli. Only a trend towards a decrease in the mean heat pain threshold was found in this study. The discrepancy between the results of this study and the previous study may be related to characteristics of the control subjects. Notably, the mean values of heat and cold pain thresholds in the control group in this study were relatively lower or higher than those in Uthaikhup et al's study but there were no significant differences in pain thresholds in cervicogenic headache between the two studies. A factor of comorbid musculoskeletal pain was not included in Uthaikhup et al's study. Decreased pain thresholds to thermal stimuli in older adults with cervicogenic headache may be associated with age-related changes in the nervous system. Evidence shows more pronounced alterations in myelinated (A delta) than unmyelinated (C) nerve fibers with increasing age (208). A delta fiber system mediates cold and pressure sensation, and together with C fibers, transmission of nociceptive cold, heat and pressure pain stimuli. Thus the altered A delta nerve activity may cause disinhibition of C fiber activity and there may be a change in central decoding of the afferent input, resulting in increased pain sensitivity. In addition, the results may suggest that heat pain threshold is due to activation of C nociceptor fibers without any significant contribution from myelinated nociceptor fibres (209).

The results of this study demonstrated no changes in pressure pain thresholds at any sites in elders with cervicogenic headache. A trend toward decreased pressure pain thresholds was observed at the tibialis anterior (a remote site) in elders with headache. However, taken together with no localized mechanical sensitivity, it is difficult to drawn whether the presence of central sensitization occurs in elders with cervicogenic headache. Further studies in larger population are needed.

A reduction of pain sensitivity at remote sites and increased responses to supra-threshold stimulation are suggestive of augmented central pain processing, which is also known as central sensitization (207). It is known that ongoing peripheral input has an influence on altered central pain processing and descending pain modulation (194, 210, 211). However, the peripheral noxious stimulus must be intense, repeated and sustained (207). 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 (11, 212). The findings from the previous and our studies support that central sensitization may not be a feature of older adults with cervicogenic headache. Additionally, several studies indicated that psychological factors influence pain sensitivity and may play a role in the development or maintenance of chronic pain conditions (200, 213). However, in this study, pain thresholds were independent of level of depressive scores. The older adults with headache had scores < 13/30 on the TGDS-L, which 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 (11). It is possible that older persons with cervicogenic headache have learned to adapt or get used to the pain.

There are some limitations in this study that need to be addressed. Sample size of this study was relatively small. The statistical power levels of the non-significant results were less than 0.8, indicating inadequate power to detect statistical significances. The current study has chosen to power on previous results concerning cold pain threshold, which seems to have a more sensitive outcome measured over the neck (204, 214). However, we do not rule out adequate power for other outcomes as a consequence of the trials being underpowered for detecting any differences between the groups. Thus, these results need to be interpreted with caution. Future studies with large sample sizes would enhance the power analysis and external validity. Evidence suggests that musculoskeletal pain is common in older adults (215). Thus it was difficult to recruit older adults who have only cervicogenic headache. 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, 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 (216). Notwithstanding, the study provides evidence for 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 mechanism associated with chronic pain syndromes (217). Further research should include conditioned pain modulation test to determine endogenous inhibitory pain pathways in older adults with cervicogenic headache.

4.5 Conclusion

This study demonstrated localized pain sensitivity over the upper cervical region in older adults with cervicogenic headache. There were no 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.