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Cervical referral of head pain in migraineurs: Effects on the nociceptive blink reflex.

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**Conflict of Interest:** Dean H Watson presents training programs to manual therapists in the assessment of the upper cervical spine in primary headache conditions; Peter D Drummond has nothing to disclose.

**Key words:** migraine, nociceptive blink reflex, central sensitisation, cervical, spinal, psychological, anxiety, fear

**Abbreviations:** nociceptive blink reflex nBR, greater occipital nerve GON, atlanto occipital AO, area under the curve AUC, trigemino cervical nucleus TCN, , diffuse noxious inhibitory control DNIC,
Abstract

Objective.— To investigate cervical, interictal reproduction of usual head pain and its effect on the nociceptive blink reflex (nBR) in migraineurs.

Background.— Anatomical and neurophysiological studies in animals and humans have confirmed functional convergence of trigeminal and cervical afferent pathways. Migraineurs often present with occipital and neck symptoms, and cervical pain is referred to the head in most cases, suggesting that cervical afferent information may contribute to headache. Furthermore, the effectiveness of greater occipital nerve (GON) blockades in migraine, and demonstrable modulation of trigeminal transmission following GON blockade, suggest an important role for cervical afferents in migraine. However, to what extent cervical afferents contribute actively to migraine is still unknown.

Methods.— The passive accessory intervertebral movements (PAIVM) of the atlanto occipital (AO) and C2-3 spinal segments of fifteen participants (14 females, 1 male; age 24 - 44 years, mean age 33.3 years) with migraine were examined interictally. During one session either the AO or C2-3 segment was examined, resulting in referred usual head pain, whilst in another session, pressure was applied over the common extensor origin (lateral epicondyle of the humerus) of the ipsilateral arm. Each intervention was repeated four times.

The nociceptive blink reflex to a supraorbital electrical stimulus was elicited ipsilaterally during both sessions before and during each intervention. The main outcome variables were the number of recorded blinks, area under the curve (AUC) and latencies of the R2 components of the nBR. Participants also rated the intensity of referred head pain and the supra orbital stimulus on a scale of 0 –10, where 0 = no pain and 10 = intolerable pain, and rated the intensity of applied pressure where 0 = ‘pressure’ and 10 = ‘intolerable pain’.
Results.— Participants reported a significant reduction in local tenderness ratings across the four trials for the cervical intervention but not for the arm ($P=.005$). The cervical intervention evoked head pain in all participants. As the cervical intervention was sustained, head pain decreased significantly from the beginning to the end of each trial ($P=.047$) and from the beginning of the first trial to the end of the last ($P=.000$). Pain evoked by the supraorbital stimulus was consistent from baseline to across the four trials ($P=.635$), and was similar for the cervical and arm interventions ($P=.072$). The number of blinks decreased significantly across the experiment ($P=.000$) and was comparable in the cervical and arm interventions ($P=.624$). Whilst the R2 AUC decreased irrespective of intervention ($P=.000$), this reduction was significantly greater for the cervical intervention than when pressure was applied to the arm ($P=.037$). Analysis of the R2 latencies revealed a notable increase across the experiment ($P=.037$). However this increase was significantly greater following the cervical than arm intervention ($P=.012$).

Conclusions.— Our findings corroborate previous results related to anatomical and functional convergence of trigeminal and cervical afferent pathways in animals and humans, and suggest that manual cervical modulation of this pathway is of potential benefit in migraine.
Introduction.-

Temporary reproduction of usual head pain when examining structures of the cervical spine is considered to be one of the key diagnostic criteria for cervicogenic headache,\textsuperscript{1,2} but cervical pain might also be important in other forms of headache. For example, we recently demonstrated reproduction of usual head pain in 95\% of migraineurs\textsuperscript{3} fulfilling the International Headache Society’s Classification criteria for migraine\textsuperscript{2} when examining the passive accessory intervertebral movements (PAIVM) of the atlanto occipital (AO) and C2-3 spinal segments.

The extremely high incidence of reproduction of headache in migraineurs could suggest an underlying cervicogenic basis for central sensitization of nociceptive second order neurons in the trigeminocervical nucleus (TCN) with subsequent hyper-excitability to afferent stimulation.\textsuperscript{4} The notion of central sensitization considers an increased barrage of afferent noxious information from C-fibres onto second-order neurons as crucial in the development of this hyper-excitability.\textsuperscript{5,6} Moreover, it has been demonstrated that stimulation of afferents from deep somatic tissues such as joints and muscles is more effective than cutaneous input in generating central hyper-excitability.\textsuperscript{7,8} More specifically, provocation of the deep paraspinal tissues at the level of the atlanto-axial (C1-2) spinal segment was shown to induce central sensitization in medullary and C1-C2 dorsal horns.\textsuperscript{9}

Together, these findings suggest that hyper-excitability of nociceptive second-order neurons in the TCN could result from noxious afferent information from dysfunctional spinal segments, thereby increasing sensitivity to subclinical afferent information from the trigeminal field. The ensuing exaggerated information is perceived as a noxious event that results in pain. In support of this possibility, central sensitization evoked by stimulation of the
greater occipital nerve (GON) resulted in occipital afferent activation of second order neurons in the TCN\textsuperscript{10} and increased excitability to dural input.\textsuperscript{11} Further support was provided by modulation of the nociceptive blink reflex (nBR) following blockade of the GON.\textsuperscript{12,13} Conceivably, occipital activation of the TCN represents the cervicogenic equivalent to application of an ‘inflammatory soup’ onto the dura which has been shown to induce central sensitization and ensuing increased sensitivity to trigeminal inputs.\textsuperscript{14}

The nBR is a trigemino-facial brainstem reflex and has been established as a valid technique for assessing central trigeminal transmission.\textsuperscript{15-18} Recently the R2 component of the nBR was examined before and after unilateral GON blocks where it was found that the R2 latency increased and area under the curve (AUC) decreased after GON blockade.\textsuperscript{12} This result provides empirical evidence for a functional influence on trigeminal nociceptive inputs from cervical afferents.

Notwithstanding the effectiveness of GON blockades for migrainuers,\textsuperscript{19-21} the mechanism(s) for the successful outcome remain uncertain.\textsuperscript{22} It has been postulated that GON blockade influences central pain processing mechanisms by modulating responses to convergent synaptic input from cervical and trigeminal nociceptive afferents.\textsuperscript{22} Another possible mechanism may be a general reduction of afferent noxious excitatory input in the TCN\textsuperscript{23} resulting in decreased R2 AUC and increased R2 latencies.\textsuperscript{12,13}

In our clinical experience, patients often report lessening of their referred, usual pain as the examination of the cervicospinal segment is sustained. The pain usually lessens (to a variable degree, but often with complete resolution) within 90 seconds. Moreover, sustaining the examination repeatedly not only results in decreasing intensity of head pain referral but also
in more expeditious resolution. Furthermore, patients presenting with allodynia frequently report that, after lessening of their referred pain, the allodynia has decreased or resolved, perhaps indicating that a pre-existing central sensitization state had diminished.

The purpose of the present study was to investigate cervical, interictal referral of usual head pain and its effect on the nBR in migraineurs. In particular, effects of passive accessory intervertebral movements (PAIVM) of the atlanto occipital (AO) and C2-3 spinal segments on referred head pain and trigeminal nociceptive activity were examined interictally. It was hypothesized that as referred head pain decreased there would be a corresponding increase in latency and decrease in the AUC of R2, reflecting a decrease in excitability of the TCN.

MATERIALS AND METHODS

Participants

Fifteen volunteers participated in the study (14 females, 1 male; age 24 - 44 years, mean age 33.3 years). All participants met the International Headache Society’s diagnostic classification criteria for migraine with or without aura, experiencing 2-8 attacks of migraine within the previous 3 months. Each participant had been free from migraine for at least 24 hours. Informed consent was obtained from all participants and the study was approved by the Ethics Committee of Murdoch University.

Passive accessory intervertebral movement (PAIVM) examination. –

The PAIVM examination was performed by a single clinician (DHW - Musculoskeletal Physiotherapist) with 22 years of experience, whose practice is limited to examination and treatment of the upper cervical spine in primary headache conditions. Intra examiner reliability was analysed using Cohen’s Kappa in a previous study which demonstrated
perfect agreement in 17 of 22 PAIVM techniques. Of the five remaining tests the lowest Kappa score was \( k=0.667, p=0.01 \), which indicated good agreement.

Critical to our study was that usual head pain could be reproduced during the cervical examination. Therefore, to exclude participants who did not develop head pain during this procedure, an ‘inclusion/exclusion’ examination was performed prior to commencing the study. This examination also established which of the AO or C2-3 spinal segments referred usual head pain most clearly and therefore which segment would be examined. The passive accessory intervertebral movement techniques have been described previously. In brief, this involves applying thumb pressure to the AO or C2-3 spinal segments.

All participants were examined in the supine position, in two sessions. Each session comprised five trials that were 90 seconds long and separated by 30 seconds. The nBR was recorded during the first trial of each session but no manual pressure was applied. Thereafter, manual pressure was applied to either the ipsilateral common extensor origin (lateral epicondyle of the humerus) of the arm or the AO or C2-3 segments and was sustained for the length of each trial. The order of the examination (i.e., cervical versus arm) alternated from one participant to the next. Participants reported reproduction of head pain with ‘yes’ or ‘no’ and rated the intensity of head pain on a scale of 0–10, where 0 = no pain and 10 = intolerable pain. Participants also rated the intensity of applied pressure where 0 = ‘pressure’ and 10 = ‘intolerable pain’.

To study trigeminal brainstem nociception and transmission, the nBR was elicited ipsilaterally using a custom-made planar concentric electrode. The electrode comprised a central wire cathode (diameter 0.5 mm), an isolation insert and an external anode ring, both 5 mm in diameter providing a stimulation area of 235.5 mm\(^2\). The electrode was placed on the
forehead 10 mm above the supra orbital groove and the nBR was recorded by two surface electrodes attached below the lower eyelid and 2–3 cm laterally. Current intensity (monopolar square wave pulses, 0.3 ms duration) was 2.3mA. Main outcome variables were the number of recorded blinks, and AUC and latencies of the R2 component of the nBR.

The nBR was recorded during both sessions, which were separated by 30 minutes. Each session comprised five trials of 8 stimuli; the inter stimulus interval varied between 12 and 18 seconds. The inter trial interval was 30 seconds.

After subtracting background noise from raw blink reflex data, latencies were established for each blink. Blinks were identified individually by inspecting each blink in the raw data files and were defined as present if the AUC was greater than background noise. Areas under the curve were assessed in the time window 27–87 ms after the stimulus.

**Statistical Approach.**—Data were analyzed using SPSS Version 16 software (SPSS Inc., Chicago, IL, USA). Local tenderness ratings were investigated in a 2 X 4 X 2 (Site [arm, neck]) X Trial [Trials 1 - 4] X Time [start, end of each trial] analysis of variance. Similar analyses were computed for supraorbital pain ratings, head pain referral, number of blinks, and R2 latency and UAC. P<0.05 was considered to be statistically significant in all analyses, and tests of statistical significance were 2-tailed. Where appropriate the Huynh-Feldt correction was used to correct for violation of the sphericity assumption.

**RESULTS**

In each case, headache was reproduced during preliminary assessment of the AO and C2-3 segments, and this referred pain ceased immediately after release of cervical pressure. None of the participants reported head pain during application of pressure to the arm.
F values for all main effects of interactions for all of the independent variables are included in Table 1.

During the cervical session, each participant reported referred head pain. As the examination technique was sustained head pain lessened in all participants, decreasing significantly from the beginning to the end of each trial (main effect for Time, $F[1,42] = 40.46; P = .000$) and from the beginning of the first trial to the end of the last (main effect for Trials, $F[2.27,34.91] = 31.01; P = .000$) (Figure 1). Also notable is that referred head pain at the end of each trial decreased progressively across the four trials when compared with ratings at the beginning of each trial (Trial x Time interaction, $F[2.49,34.91] = 3.11, P = .047$). The referred head pain eased immediately on cessation of the technique at the end of each trial in all participants.

When averaged across the four trials, mean ratings of tenderness to thumb pressure were identical across the four trials for both interventions ($F[3,42] = .00; P = 1.0$). However, participants reported a significant reduction in tenderness across trials during the cervical but not the arm intervention (Site x Trial interaction, $F[3,42] = 4.92; P = .005$) (Figure 2).

Mean ratings of the supra orbital stimulus were similar across the five trials ($F[4,56] = .64; P = .635$) and were comparable for cervical and arm interventions (Site x Trial interaction, $F[3.07,42.92] = 2.49; P = .072$) (Figure 3).

To establish a baseline for R2, blinks were elicited in the absence of either the cervical or arm intervention during the first trial. Cervical and arm interventions were then applied in the ensuing four trials. The number of blinks decreased significantly across the five trials (main
effect for Trials, \( F[4,56]=25.23; \ P=0.000 \) and was comparable for the cervical and arm interventions (Site x Trial interaction, \( F[4,56]=0.66; \ P=0.624 \) (Figure 4).

Whilst the R2 AUC decreased irrespective of intervention (main effect for Trial, \( F[4,32]=13.41; \ P=0.000 \)), this reduction was significantly greater for the cervical than arm intervention (Site x Trial interaction, \( F[4,32]=2.91; \ P=0.037 \) (Figure 5).

Analysis of the R2 latencies revealed a notable increase across the five trials (main effect for Trials, \( F[4,24]=3.02; \ p=0.037 \)). However, this increase was significantly greater for the cervical than arm intervention (Site x Trial interaction, \( F[4,24]=4.07; \ p=0.012 \) (Figure 6).

No participant experienced a migraine attack for at least 48 hours following the study.

**DISCUSSION:**

In our previous study, local and referred head pain was reproduced during manual pressure over the atlas or C2 in 95% of migraineurs.\(^3\) Similarly, in the present study, head pain was reproduced during this procedure in all 15 participants. Thus, referral of head pain from upper cervical structures could be an important but under-recognised characteristic of migraine. Furthermore, after repeated application of manual pressure, local and referred head pain decreased in parallel with decreases in the trigeminal nociceptive blink reflex (i.e., a decrease in the AUC and increase in latency of the ipsilateral R2 waveform). To our knowledge this is the first time a manual cervical examination technique has been shown to influence trigeminal nociceptive neurotransmission.

Spinal mobilisation is typically applied when dysfunctional areas of the vertebral column are
found. Clinicians utilising manual therapy identify spinal dysfunction based upon various features; amongst these are the ability to reproduce local and referred pain, and restrictions in spinal joint motion.\textsuperscript{31,32} The clinician’s objective in applying manual techniques is to restore normal motion and normalise afferent input from the neuro-musculoskeletal system.\textsuperscript{30} Despite clinical evidence for the benefits of spinal mobilisation, the biological mechanisms underlying the effects of spinal mobilisation are not known.\textsuperscript{34-36} One of the principal rationales for manual therapy intervention is that an ongoing barrage of noxious sensory input from biomechanical spinal dysfunction increases the excitability of neurons or circuits in the spinal cord.\textsuperscript{37-39} Mechanoreceptors including proprioceptors (muscle spindles, both primary and secondary endings and Golgi tendon organs), low- and high-threshold mechanoreceptors, high-threshold mechano-nociceptors and high-threshold polymodal nociceptors\textsuperscript{40} within deep paraspinal tissues react to mechanical deformation of these tissues.\textsuperscript{41} A significant effect of this ‘biomechanical remodeling’ could be restoration of zygapophyseal joint mobility and joint ‘play’,\textsuperscript{33} precisely the intention of the techniques used in this study. Thus, biomechanical remodeling resulting from mobilisation may have physiological ramifications, ultimately reducing nociceptive input from receptive nerve endings in innervated paraspinal tissues.\textsuperscript{37,38,41}

Our findings of decreased AUC and increased latency of R2 during the cervical intervention are supported by a fMRI study in which manual therapy was administered to the ankle joints of rats following capsaicin injection. Subsequent to mobilisation there was decreased activation of the dorsal horn.\textsuperscript{42} By analogy, upper cervical afferents may have an excitatory influence on trigeminal circuits in migraine sufferers that can be reduced by reproduction and lessening of usual head pain.

The reduction in the nBR during spinal mobilisation is consistent with previous studies
demonstrating a functional connectivity between the cervical and the trigeminal system in the
trigeminocervical complex of the brainstem.\textsuperscript{9-12,43-45} This inhibitory effect may be due to a
general reduction of afferent cervical nociceptive/excitatory input in the trigeminocervical
complex as result of biomechanical remodeling, perhaps restoring joint mobility and joint
play,\textsuperscript{33} as inhibition of R2 was more significant than during the arm intervention. Therefore,
the highly significant reduction in head pain referral during the cervical intervention could be
a clinical correlate of lessening central sensitization of the TCN. In particular, it is
conceivable that palpation and stretch of dysfunctional cervical paraspinal tissues elicits
tenderness that lessens as remodeling occurs.\textsuperscript{37,38,41} This could explain why tenderness
ratings decreased during the cervical intervention and not the arm for, presumably,
participants’ arm tissues were not dysfunctional and subject to remodeling.

However, the perception of pain is not only determined by the intensity of the afferent pain
signal (nociception).\textsuperscript{46} Nociceptive inputs to the dorsal horn of the spinal cord are also
influenced by potent endogenous descending inhibitory and facilitatory processes from
supraspinal regions. This bidirectional, central control incorporates a frontal, limbic,
brainstem and spinal cord neuronexus\textsuperscript{47-50} that is driven primarily by noxious inputs and
associated emotional responses. Importantly, this includes spinal cord activity because the
spinally-mediated nociceptive flexion reflex is influenced by central pain modulation
processes.\textsuperscript{51} Whilst the exact mechanisms responsible for emotional modulation of pain are
not fully understood, heightened anxiety appears to increase sensitivity to pain
(hyperalgesia),\textsuperscript{52-69} whilst moderate fear inhibits pain (hypoalgesia).\textsuperscript{52,70-78} This suggests that
anticipation of an unpredictable, threatening intervention could result in enhanced pain,
whilst hypoalgesia results from exposure to a predictable, threatening event (fear).\textsuperscript{52}
As we did not assess the participants’ psychological state, we are unsure whether this changed of the course of the experiment. Nevertheless, it seems unlikely that psychological factors had a major influence on our findings for the following reasons. First, participants were included only if usual head pain could be produced when stressing either the AO or C2-3 segments - the ‘inclusion/exclusion’ session. In the case of head pain referral, both segments were examined (prior to the experimental sessions) to ascertain which segment reproduced usual head pain most clearly. Thus, participants experienced reproduction of their usual head pain, which ceased immediately on cessation of the technique (i.e., essentially participants were ‘cued’ to believe that the procedures were not threatening). Second, participants, armed with the knowledge that they could terminate the experimental session at any time, were in control, further lessening the role of psychological factors.79-84 Third, pain ratings to the supraorbital stimuli were comparable for the cervical and arm interventions and remained unchanged across the trials. This dissociation between pain perception and R2 activity supports the possibility that the reductions in referred head pain, cervical tenderness and inhibition of R2 were due to a specific ‘cervical’, neurophysiological effect, rather than psychological influences.

Another possible mechanism for the inhibitory effect on pain demonstrated in our study is that of placebo. Previous work has shown that the prospect of reduced pain can reduce the pain reported in response to a noxious stimulus.85-89 The ‘inclusion/exclusion’ session provided an expectation that head pain would increase during the interventions and cease immediately after cessation of the technique. However, participants had no prior expectation of the likely course of referred head pain as the technique was sustained. Accordingly, we considered that any placebo effect was minimal.
An additional potential inhibitory mechanism is diffuse noxious inhibitory controls (DNICs). The DNIC process involves inhibition of neurons in the dorsal horn of the spinal cord in response to nociceptive stimuli applied to any part of the body, unconnected to their facilitatory fields. However if DNICs were operational we would have expected identical effects on the nBR during the arm and cervical interventions as mean ratings of local tenderness were the same.

**Limitations.** –

Although standardisation of pressure clearly is important, for it to be achieved during application of techniques used in this study and in a PAIVM examination, pressure algometers would need to be devised which not only attach to the thumb but are sufficiently fine to allow for skilled palpation and perception of mobility. The absence of such a device in our study could be regarded as a shortcoming. The sample size could also be considered a limitation; nevertheless, effects of the cervical intervention were strong enough to be detected even in our small sample. Perception and self-reporting of pain clearly involve psychological influences such as anxiety and fear. These influences need to be investigated in future studies.

**Conclusions.** –

To our knowledge this is the first time cervical manual examination techniques have been shown to influence trigeminal nociceptive neurotransmission. Our results suggest that cervical spinal input contributed to lessening of referred head pain and cervical tenderness, and inhibition of R2. These findings support the concept that noxious cervical afferent inputs contribute to headache in migraine sufferers. They corroborate previous results related to anatomical and functional convergence of trigeminal and cervical afferent pathways in
animals and humans, and suggest that manual modulation of the cervical pathway is of potential benefit in migraine.

STATEMENT OF AUTHORSHIP

Category 1
- (a) Conception and Design Peter Drummond, Dean Watson
- (b) Acquisition of Data Dean Watson
- (c) Analysis and Interpretation of Data Peter Drummond, Dean Watson

Category 2
- (a) Drafting the Manuscript Dean Watson, Peter Drummond
- (b) Revising It for Intellectual Content Dean Watson, Peter Drummond

Category 3
- (a) Final Approval of the Completed Manuscript Peter Drummond, Dean Watson
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Figure 1. Referral ratings stratified by Trials. Note that not only did referral ratings decrease, but the values at the end of each trial decreased progressively across the four trials when compared with the values at the start of each trial.

Figure 2. Tenderness ratings stratified by Trials. Note that cervical tenderness ratings decreased progressively, whilst those for the arm remained unchanged.
Figure 3. Supra orbital ratings stratified by Trials. (Trials 1 = baseline i.e., no intervention). Note that the ratings remained unchanged across the trials for both sites.

Figure 4. Number of nBR stratified by Trials. Note the decreasing number of blinks across the Trials for both sites.
Figure 5. R2 areas under the curve (AUC) stratified by Trials. (Trial 1 = baseline i.e., no intervention). Of note is the significant decrease of AUC during the cervical, but not the arm intervention.

Figure 6. R2 Latencies stratified by Trials. (Trial 1 = baseline i.e., no intervention). Of note is the significant increase of latencies during the cervical, but not the arm intervention.
Table 1. F ratios for the main effects and interactions of the dependent variables.

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<th>Supra orbital ratings</th>
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<td>Site x Trials</td>
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AUC = area under the curve
a 4 intervention trials
b baseline + 4 intervention trials
* p<0.05; ** p<0.01; *** p<0.001