Universidade de São Paulo
Faculdade de Medicina de Ribeirão Preto

2017

Cervical muscle strength and motor control assessment using dynamometry and surface electromyography in women with migraine and chronic migraine: a controlled study

PPGRDF
PROGRAMA DE PÓS-GRADUAÇÃO EM REABILITAÇÃO E DESEMPENHO FUNCIONAL
FMRP-USP

Lidiane Lima Florencio

Tese

LIDIANE LIMA FLORENCIO

Cervical muscle strength and motor control assessment using dynamometry and surface electromyography in women with migraine and chronic migraine: a controlled study

Thesis presented to Ribeirão Preto Medical School of University of São Paulo to obtain a doctoral degree (PhD) in Sciences.

Area: Physical Therapy

Advisor: Professor Débora Bevilaqua Grossi, PhD.

Ribeirão Preto
2017

LIDIANE LIMA FLORENCIO

Avaliação da força máxima e do controle motor da coluna cervical pela dinamometria e pela eletromiografia de superfície em mulheres com migrânea e migrânea crônica: estudo controlado

Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Área de concentração: Fisioterapia

Orientador: Profa. Dra. Débora Bevilaqua Grossi

Ribeirão Preto
2017

Publication listing

Ribeirão Preto Medical School of University of São Paulo

Florencio, Lidiane Lima

Cervical muscle strength and motor control assessment using dynamometry and surface electromyography in women with migraine and chronic migraine: a controlled study. Ribeirão Preto, 2017.

p.155 : il.23 ; 30 cm

Doctoral Thesis presented to the Ribeirão Preto Medical School/ USP – Post Graduation Program of Rehabilitation and Functional Performance, Area: Physical Therapy.

Advisor: Bevilaqua Grossi, Débora.

1. Migraine Disorders, 2. Spine, 3. Surface electromyography,
4. Pain, 5. Craniocervical flexion test

Catalogação da Publicação

Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo

Florencio, Lidiane Lima

Avaliação da força máxima e do controle motor da coluna cervical pela dinamometria e pela eletromiografia de superfície em mulheres com migrânea e migrânea crônica: estudo controlado. Ribeirão Preto, 2017.

p.155 : il.23; 30 cm

Tese apresentada à Faculdade de Medicina de Ribeirão Preto/ USP – Programa de Pós Graduação em Reabilitação e Desempenho Funcional, Área: Fisioterapia.

Orientadora: Bevilaqua Grossi, Débora.

1. Transtornos de Enxaqueca, 2. Coluna Vertebral, 3. Eletromiografia de superfície, 4. Dor, 5. Teste de flexão craniocervical

APPROVAL PAGE

Name: Lidiane Lima Florencio

Title: Cervical muscle strength and motor control assessment using dynamometry and surface electromyography in women with migraine and chronic migraine: a controlled study

Thesis presented to Ribeirão Preto Medical School of University of São Paulo in the Department of Biomechanics, Medicine and Locomotor Apparatus Rehabilitation to obtain a doctoral degree (PhD).in Sciences by the Post Graduation Program Rehabilitation and Functional Performance. Area: Physical Therapy.

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Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo junto ao Departamento de Biomecânica, Medicina e Reabilitação do Aparelho Locomotor para obtenção do título de Doutor em Ciências pelo Programa de Pós Graduação em Reabilitação e Desempenho Funcional. Área: Fisioterapia.

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Dedico com todo meu amor e gratidão

aos meus pais, Antônio Carlos e Maria Elídia, ao meu irmão Thiago e ao pequeno Davi que juntos são minha fortaleza, inspiração e motivação.

Acknowledge/ Agradecimentos

Agradeço a Deus por me guiar e proteger ao longo de toda a jornada que culmina na finalização dessa tese. Hoje, ao refletir sobre minha trajetória, sinto-me muito grata por todas as oportunidades de desfrutar das pequenas conquistas diárias e de crescer diante das dificuldades. Tenho fé nos Seus planos e confiança na Sua vontade para continuar trilhando meu caminho.

Agradeço à minha orientadora Profa. Débora. Por força do costume de um eterno pós-graduando, fui buscar uma citação que expressasse melhor o que gostaria de te dizer. Começo, então, por Paulo Freire cuja afirmação contempla a meu ver, algumas de suas melhores qualidades: "*A educação é um ato de amor, por isso, um ato de coragem. Não pode temer o debate. A análise da realidade. Não pode fugir à discussão criadora, sob pena de ser uma farsa."* Você sem dúvida alguma sabe educar com maestria. Ao longo desses 11 anos, fui testemunha diversas vezes do seu amor pelas pessoas e pela profissão, além da sua coragem de enfrentar o que quer que seja necessário, principalmente quando se trata de interesses de um grupo. Obrigado por me ensinar, por me acolher e por abrir as portas, as janelas e meus olhos para a grandeza e beleza desse mundo afora.

Agradeço à minha coorientadora Profa. Anamaria por me inspirar com sua dedicação e afinco na busca constante de conhecimento e novos desafios. Você deflagrou por diversos momentos minha curiosidade e teve papel importante no meu aprofundamento teórico para a formulação dessa tese. Mas, acima de tudo, agradeço pelo carinho e pelo cuidado com que me trata. Não poderia ter tido parceria melhor que a sua.

Meu desenvolvimento científico e aprimoramento teórico também foram impulsionados pela colaboração ativa e constante do Prof. Marcelo Bigal, Profa. Fabíola Dach, Prof. César Fernández de las Peñas, Tenysson Will de Lemos e Gabriela Ferreira Carvalho. Meu sincero agradecimento por todas as discussões e por todo conhecimento compartilhado.

Agradeço à FAPESP pelo apoio financeiro que viabilizou a execução e divulgação dos projetos envolvidos nessa tese. Para que todos os projetos se concretizassem, fui também agraciada pela companhia e auxílio de diversas pessoas as quais agradeço pontualmente: às alunas de Iniciação Científica Gabriela Tollentino, Carolina Almeida e Ana Paula Carnevalli; à equipe de neurologistas contratados e residentes do Ambulatório de Cefaleia e Algias Craniofaciais do HCRP-FMRP/USP; à Gabi Ferracini, que não somente me ajudou nas coletas, mas também me acompanhou na tarefa de encarar a experiência de pesquisar e morar

em um país diferente do nosso; à equipe e amigos da Universidad Rey Juan Carlos, especialmente à Maria sem a qual nossas coletas não teriam sido possíveis; e por fim, a todos os voluntários que dedicaram seu tempo e pelos quais somos tão engajados em seguir na missão de pesquisar.

Agradeço aos meus amigos e colegas do LAPOMH Maria Cláudia, Carina, Denise, Jaqueline, Daiane, Gabriel, Isadora, Izabela, Ana Cristina, Thiele, Harumi, Cesário, Marília, Mariana, Samuel, Marcela, Eduardo, Ramón, Walter e todos aqueles que por descuido não me lembrei de citar. Nossas conversas, risadas, churrascos, reuniões temáticas, choros e angústias em comum me fez crescer tanto pessoal quanto profissionalmente. A união e o espírito coletivo que temos faz toda diferença e me faz valorizar ainda mais meu período na pós-graduação ao lado de vocês. Um agradecimento especial ao grupo de Cefaleia (ICs e Pós-graduandos) por todos os ensinamentos proporcionados a mim.

Agradeço aos meus lindos amigos Luiz, Fabiana, Catia, Letícia, Ana Paula,Thaís, Camila, Guilherme, Tainan, Paula, Lilian e Cláudia. Sei que sempre posso contar com vocês, não importa a distância. Obrigado por tornar meus dias mais felizes e minha caminhada mais leve.

Agradeço ao Domingo, uma das minhas melhores surpresas da vida. O seu amor, carinho, cuidado e suporte foram essenciais nessa etapa final. Você me ensina diariamente a ver a vida com mais alegria e a valorizar o amor e as pessoas as quais amamos.

Agradecer à minha família por último é proposital. Gostaria que quem estivesse lendo (inclusive os mesmos), saiba que tudo o que eu citei antes sobre ser capaz de viver, encarar, aprender e conhecer não seria possível se não fosse a base forte que eu tenho. Meus pais me ensinaram a persistência, a humildade e a determinação; são eles que me estimulam diariamente a traçar novos sonhos e sair em busca deles. Meu irmão é o meu melhor amigo e me ensinou muito sobre dividir, acalentar e ser presença constante para aqueles que amamos. Tudo que sou e tenho não faria sentido se não tivesse vocês para compartilhar. Deus foi muito bondoso ao me colocar ao lado de vocês.

“*Onde há amor e sabedoria, não tem temor e nem ignorância*”.

São Francisco de Assis

Abstract

Florencio LL. Cervical muscle strength and motor control assessment using dynamometry and surface electromyography in women with migraine and chronic migraine: a controlled study. [thesis]. São Paulo: University of São Paulo, Ribeirão Preto Medical School , 2017. 155p.

Objectives: to verify if women with migraine present altered neck muscles function and altered muscle activity in comparison to non-headache subjects. Moreover, we aimed to identify if there is any relationship between neck muscles dysfunction and the chronicity of migraine attacks. **Methods:** women with migraine, stratified by episodic and chronic, and age-matched non headache women were the subject of the current thesis. Neck pain related-disability was assessed by the Neck Disability Index. Neck muscles strength was assessed by a customized hand-held dynamometer. Myoelectrical signals of the sternocleidomastoid, anterior scalene, splenius capitis and upper trapezius were assessed using surface electromyography. Experimental conditions involved maximal isometric voluntary contractions in flexion, extension and lateral bending directions and; craniocervical flexion test, a low load test applied to verify deep cervical flexors ability to supply adequate cervical spine stability. Finally, identification of myofascial trigger points and head and cervical posture photogrammetric evaluation were made in order to be correlated to the muscles electrical activity in the craniocervical flexion test. **Results:** Although both groups presents high prevalence of neck related disability, subjects with chronic migraine are more likely to report neck related disability, especially the most disabling forms, than episodic migraine. Episodic migraine demonstrated to different neck muscle control only under maximal voluntary tasks. Chronic migraine presented alterations in comparison with controls at maximal conditions, i.e., lower extension force; more time to produce maximal force; greater antagonist coactivation and greater fatigability. During craniocervical flexion test, chronic migraine also differs from control group presenting greater activity of neck extensors. Presence of active trigger points in neck muscles and extended head posture can influence the neck muscles activity during the craniocervical flexion test. **Conclusions:** migraine is associated to a deterioration of neck muscles functions and to an altered motor control. We can assume an interaction between chronicity of migraine frequency and cervical dysfunction, specially related to neck extensors. More severe disabilities and the majority of the altered function or motor control could only be evidenced in the chronic form.

Key words: Migraine Disorders, Spine, Surface electromyography, Pain, Craniocervical flexion test

Resumo

Florencio LL. Avaliação da força máxima e do controle motor da coluna cervical pela dinamometria e pela eletromiografia de superfície em mulheres com migrânea e migrânea crônica: estudo controlado [tese]. São Paulo: Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, 2017. 155p.

Objetivos: verificar se mulheres com migrânea apresenta alteração na função e atividade dos músculos do pescoço quando comparados a mulheres sem cefaleia. Ainda, objetivamos identificar se há relação entre disfunção cervical muscular e a cronicidade da frequência de crises migranosas. **Materiais e métodos:** mulheres com migrânea, estratificada entre episódica e crônica, e mulheres sem cefaleia com idade semelhante foi o objeto de estudo dessa tese. Foi investigada a incapacidade relacionada à dor cervical pelo questionário *Neck Disability Index* e a força muscular cervical utilizando um dinamômetro manual customizado. Ainda, a atividade elétrica dos músculos esternocleidomastoideo, escaleno anterior, esplênio da cabeça e trapézio superior foi verificada pela eletromiografia de superfície. Os procedimentos experimentais foram contração isométrica voluntária máxima em flexão, extensão e inclinação lateral; e o teste de flexão craniocervical, que avalia a habilidade dos músculos flexores cervicais profundos em prover adequada estabilidade para esse segmento. Por fim, a identificação de pontos gatilhos nos músculos cervicais e a avaliação da postura da cabeça e do pescoço por foto foram realizadas a fim de correlacionar os achados com a atividade eletromiográfica. **Resultados:** embora ambos os grupos de migrânea tenham apresentado alta prevalência de incapacidade relacionada à dor cervical, a migrânea crônica apresenta maior risco de relatar incapacidades mais severas em relação a migrânea episódica. O grupo de migrânea episódica apresentou controle muscular cervical alterado em condição de contração voluntária máxima. Já o grupo migrânea crônica apresentou alterações sob condições máximas, como por exemplo, redução da força dos extensores, mais tempo para gerar pico de força em flexão e inclinação lateral, maior coativação do antagonista e maior susceptibilidade à fadiga. Ainda, durante o teste de flexão craniocervical, o grupo migrânea crônica apresentou maior atividade dos extensores indicando alteração no controle motor. A presença de pontos gatilhos nos músculos do pescoço e a postura em extensão de cabeça pode influenciar a atividade elétrica dos músculos cervicais durante a execução do teste de flexão craniocervical. **Conclusões:** a migrânea está associada a uma deteriorização da função e do controle motor cervical. Podemos assumir ainda que há uma interação entre a cronicidade da

frequência das crises migranosas e a disfunção muscular cervical, especialmente relacionada aos extensores. Incapacidades mais severas e a maioria das disfunções musculares e alteração no controle motor só puderam ser evidenciadas para o grupo com migrânea crônica.

Palavras-Chave: Transtornos de Enxaqueca, Coluna Vertebral, Eletromiografia de superfície, Dor, Teste de flexão craniocervical

Abbreviation List

ANCOVA: analysis of co-variance

ANOVA: analysis of variance

AS: anterior scalene

BMI: body mass index

CCF: cranio-cervical flexion

CCFT: craniocervical flexion test

CGRP: calcitocin gene-related peptide

CI: confidence interval

CM: chronic migraine

CMRR: common mode rejection ratio

CNS: central nervous system

CSD: Cortical Spreading Depression

CV: cranio-vertebral angle

EM: episodic migraine

EMG: electromyography

FAPESP: São Paulo Research Foundation

FFT: fast Fourier Transform

HHD: hand held dynamometer

ICC: intraclass correlation coefficient

ICHD-3: International Classification of Headache Disorders criteria, third edition

MDF: Median frequency

MIVC: maximal isometric voluntary contractions

MoH: medication overuse headache

MVC: maximal voluntary contraction

NDI: Neck Disability Index

NPRS: numeric pain rate scale

PBU: pressure biofeedback unit

RMS: root mean square

RR: Relative Risk

SC: splenius capitis

SCM: sternocleidomastoid

SD: standard deviation

SPLEN: splenius capitis

TrP: trigger points

UT: upper trapezius

Summary

1 Theoretical contextualization

Migraine is a common disabling primary headache disorder characterized by recurrence and manifested in attacks lasting 4–72 hours. Headache is typically characterized by unilateral location, pulsating quality, and moderate or severe intensity. It is aggravated by routine physical activity and associated with nausea and/or phonophobia and photophobia. When subjects present with headaches on 15 or more days per month for more than three months, with features of migraine on at least eight days per months, it is diagnosed as chronic migraine.[1] Each year, 2.5% of subjects with migraine progress to the chronic form and the population prevalence of chronic migraine is about 2%.[2]

Migraine is a recognized burdensome worldwide condition ranked by the World Health Organization in 2010 as the third most prevalent disorder, affecting around 15% of the population, and is the sixth-highest specific cause of disability worldwide.[3,4] North, Central, and South America are cited as the most prevalent continents[4] and, in Brazil, prevalence estimation is around 15% of the population.[5]

Hyperexcitability of the central nervous system (CNS) of subjects with migraine is responsible for the clinical manifestations of a migraine attack.[6,7] Didactically, a migraine attack can be divided into four phases: [8]

- 1 – Premonitory symptoms (prodromes): symptoms that precede other symptoms of the migraine attack by 2–48 h, and forewarn of the other symptoms to come[9]
- 2 – Aura: transient focal neurological symptoms with 5–60 min of duration that usually are accompanied, or followed within 60 minutes, by headache[1]
- 3 – Headache and associated symptoms: typical migraine headache characteristics as above-mentioned accompanied by a variety of autonomic symptoms (nausea, vomiting, yawning); affective symptoms (depression and irritability); cognitive (difficulty in finding words, transient amnesia) and sensory symptoms (photophobia, phonophobia, osmophobia, muscle tenderness, and cutaneous allodynia)[10]
- 4 – Resolution phase (postdromes): absence of headache symptoms that persists for 1–2 days after headache resolution[11]

These phases do not necessarily occur in all migraine attacks and sometimes they can overlap.[12] A large variety of premonitory and resolution symptoms can be cited. They include

hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain, difficulty in concentrating, photophobia, phonophobia, nausea, and blurred vision.[10]

The characteristics of a migraine attack demonstrate that several structures and functions of the CNS are involved in migraine pathophysiology. Nowadays, migraine is viewed as a complex neurological disorder that affects the regulation structures and function of multiple cortical, subcortical, and brainstem areas responsible for autonomic, affective, cognitive, and sensory functions.[10]

Migraine pathophysiology is not totally understood. It is recognized as a primary disorder of brain excitability characterized by deficient regulation of the excitatory/inhibitory balance during cortical activity. This imbalance may contribute to the ignition of the cascade of a migraine attack and also contributes to the sensory dysfunction in the information process during the interictal phase.[13]

The most recent evidence suggests that a migraine attack initiates centrally, considering the characteristics of the premonitory symptoms.[10] The hypothalamus, cortex, and limbic system would play an important role in this phase.[14] According to Burstein et al. (2015),[10] there are two main hypotheses grounded in the literature to describe it: (1) hypothalamic neurons would be able to activate meningeal nociceptors by altering the balance between parasympathetic and sympathetic tone in the meninges; or (2) hypothalamic neurons and brainstem structures would regulate the transmission of nociceptive trigeminovascular signals from the thalamus to the cortex by setting points for the allostatic load. This would explain why some intrinsic and extrinsic factors only trigger headache eventually.

Subsequently, the central mechanism that would occur during a migraine attack is cortical spreading depression (CSD), described first by Leão (1944),[15,16] which is the generator of the aura. CSD is a slow wave of depolarization/excitation followed by hyperpolarization/inhibition in cortical neurons and glia.[16–18] The CSD will promote a transient reduction of the cerebral blood flow[19] and then activate the trigeminovascular system, which will be responsible for the initiation of the headache.

It has been speculated that, for those subjects who did not present aura, the CSD occurs in silent areas or the activation of the trigeminovascular system is provoked by glial cells.[1,19] Activation of the trigeminovascular system is believed to be mediated by the

calcitocin gene-related peptide (CGRP) and substance P release, generating a neurogenic inflammation in the meningeal vessels.[20] Augmented concentration of proinflammatory substances will alter the local molecular environment and promote a peripheral sensitization, facilitating the transduction of electrical signals through the trigeminovascular pathway.[21] The activation of second- and third-order central trigeminovascular neurons will activate areas of the brainstem, forebrain, and somatosensory cortex responsible for the associated symptoms and headache sensation. In most migraine patients, second- and third-order neurons also become sensitized, leading to the phenomena of central sensitization.[10]

Once central sensitization is established, the spontaneous activity of central neurons will increase, their receptive fields expand, and innocuous mechanical and thermal stimulation of cephalic and extracephalic skin areas will be perceived as painful. This is a phenomenon called cutaneous allodynia.[22] Patients who manifest cutaneous allodynia are predisposed to progress to the chronic form.[23,24]

Although diagnosis of episodic and chronic migraine is distinguished by frequency of headaches, there is a debate in neurology about whether they are the same entity or distinct disease processes, considering the differences in sociodemographic and comorbid profiles.[25,26] Additionally, they present distinct changes in the brain structures, but it is still unclear whether frequent migraine attacks lead to more extensive damage or whether more severe structural aberration is a risk factor for a more severe type of migraine.[26]

The pathophysiologic migraine mechanism of interest for this thesis is the abnormal sensory processing, along with central sensitization, especially at the second-order neurons situated in the trigeminal caudal nucleus. At this nucleus, the sensory inputs from meningeal vessels, trigeminal nerve, and upper cervical roots converge to be processed, regulated, and/or coded through the trigeminovascular pathway.[27] As the second-order neurons become sensitized, neck pain may consequently be facilitated. Together, both mechanisms would support the coexistence of migraine and neck pain. Thus a vicious cycle can be maintained, because neck pain can be a trigger for a migraine attack,[28] and a repetitive state of headache can promote even more damage to the brain structures and function, which makes the subject susceptible to chronification.[29]

Neck pain affects around 76% of migraineurs[30] and its prevalence increases proportionally to the increase in frequency of migraine attacks.[31] Neck pain/stiffness can

appear as a premonitory symptom, accompanying a migraine attack or even facilitated in the interictal phase.[28,30–37] Rates of neck pain self-report as an associated symptom can be even greater than the frequency of nausea, a component of the diagnostic criteria.[38] The presence of neck pain in a migraine attack can delay or reduce the efficacy of an acute pharmacological intervention and also predict more severe migraine-related disability.[38,39]

Additionally, migraine has been associated with several cervical dysfunctions such as reduced range of motion,[40–42] hypersensitivity to articular and muscle palpation,[43–45] greater presence of myofascial trigger points,[41,46] and posture changes, especially in the craniocervical area.[41,47]

Motor control adaptations and altered muscle activity are expected to occur in subjects who experience neck pain.[48] Acute adaptations are considered beneficial, because they aim to protect the structures affected; however, persistent adaptation is considered to be maladaptative, that is, changes that might contribute to the chronification of pain conditions.[48,49] Moreover, altered motor control may lead to peripheral structural changes in the neck muscles.[50]

There is evidence that neck muscle motor control and performance are altered in subjects with nonspecific or chronic neck pain. Increased activity of superficial neck flexors can be observed to compensate for the inability or delay of the deep neck flexors in sustaining craniocervical flexion, indicating a deficit in cervical segmental stabilization.[51–55] Also, the neck muscles of subjects with neck pain seem to present greater fatigability,[56] difficulty in relaxing,[57] and greater antagonist co-activation associated with force reduction, intensity of neck pain, and severity of neck-related disability.[58]

Despite the close relationship between migraine and neck pain, to the best of our knowledge investigations regarding neck muscle function and electrical activity of subjects with migraine are scarce in the current literature.[59–63] Thus far, repercussions in the neck muscle force production of migraineurs is conflicting.[59,60] No compensation of the superficial neck flexors seems to occur in order to stabilize this segment,[59,62] and greater antagonist coactivation during maximal effort has been reported in adolescents.[60] However, the association between the chronicity of migraine attacks' frequency and neck-related disability and neck muscle activity/function has never been investigated.

The current thesis will present several articles developed during the doctoral project and with our collaborators in a temporal progression about the investigation of the relationship between neck pain and migraine, focused on neck function and neck muscle activity. First, we verified the relationship between neck-related disability and migraine chronification (Study 1). Secondly, we assessed the neck muscle function and activity of subjects with episodic and chronic migraine and compared them with healthy controls (Study 2). Finally, we investigated the relationship between neck muscle activity and some musculoskeletal conditions such as head and neck posture or triggers points (Study 3).

Our main objective was to verify whether subjects with migraine present altered neck muscle function and altered muscle activity in comparison to non-headache subjects. Moreover, we aimed to identify whether there is any relationship between neck muscle dysfunction and the chronicity of migraine attacks. Our hypothesis was that migraineurs present cervical muscles impairments and related disability, with more severe presentation in the chronic subform.

Knowing the neck muscle adaptation response to pain in subjects with migraine and its relation to the chronification of the migraine attacks would help to suggest more specific options for therapeutic interventions. For example, strengthening exercises, cervical segmental stabilization, or motor control strategies could interfere with the overall impact of migraine and prevent its chronification by reducing peripheral stimuli that might contribute to the perpetuation of the condition.

2 Material and Methods

2.1 Study 1 (Article 1)

Study design and ethical aspects

This study has a cross-sectional design and was approved by *Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto* (process no. 14100/2010) (Attachment 1).

Sample

Participants were selected among the patients who had a neurologist appointment at the Headache and Craniofacial Pain Ambulatory of the *Hospital das Clínicas de Ribeirão Preto* from August 2010 to September 2012. The sample consisted of women with an age range from 18 to 65 years, diagnosed with migraine with or without aura (called as episodic migraine), or chronic migraine. Headache diagnoses were assigned by neurologists according to the second edition of the International Classification of Headache Disorder criteria.[64]

Exclusion criteria were the presence of concomitant headache diagnosis, history of cervical trauma, and/or self-report of cervical diseases. Patients agreeing to participate and fulfilling the criteria were enrolled.

Among the eligible 519 volunteers, 169 met the criteria: 104 had episodic migraine (mean age = 36 years, SD = 10.7) and 65 had chronic migraine (mean age = 38 years, SD = 10.2). The sample size was calculated to yield 90% of power for detecting a 10% difference at 5% significance. The minimum sample size was 60 participants per group.

Questionnaires

A non-blinded examiner interviewed the participants about the headache characteristics, such as frequency, time of migraine onset, and headache intensity (using a numerical scale ranging from 0 to 10).

Disability due to neck pain was assessed in all subjects by the Neck Disability Index questionnaire and classified as none (0-4 points), mild (5-14 points), moderate (15-24 points), severe (25-34 points), or complete disability (35 points or more).[65,66] This is the most

recommended tool to assess disability due to neck pain with acceptable reliability; an intraclass correlation coefficient (ICC) ranging from 0.50 to 0.98; and adequate internal consistency, validity, and responsiveness.[67,68]

2.2 Study 2 (Articles 2, 3, and 4)

Study design and ethical aspects

This cross-sectional study and the methods applied to assessment were approved by the *Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto* (process number 16692/2012) (Attachment 2). All subjects signed the informed consent form.

Sample

Subjects were recruited from the Headache and Craniofacial Pain Ambulatory of the *Hospital das Clínicas de Ribeirão Preto* between January to October 2014. Inclusion criteria were: woman with migraine aged between 18 and 55 years old. Migraine diagnosis by an experienced neurologist followed the third edition of International Headache Society criteria.[1] To avoid overlapping between groups, we included individuals with episodic migraine with less than 10 days of headache per month, while chronic migraine had at least 15 days of headache per month. In addition, a control group without headache history matched by age to the migraine group was also recruited among patients' companions and university staff. Exclusion criteria included: concomitant presence of other headaches types; medication overuse; history of neck/head trauma (i.e., whiplash); history of cervical herniated disk or cervical vertebrae arthrosis according to medical records; anesthetic block in the past month; and pregnancy.

From 116 eligible subjects with migraine, 14 did not accept to participate and another 50 were excluded. Reasons were: comorbid headaches (n=19); receiving anesthetic block in the past three months (n=16); reporting previous head/neck trauma (n=8); or unavailability to attend the appointment (n=7). Therefore, migraine groups were composed of 31 subjects with episodic migraine (33 years old; SD: 11.2) and 21 with chronic migraine (34 years old; SD: 9.8). Thirty-one women without headache in the past year comprised the control group (31

years old; SD: 9.1). *A priori* sample size calculation was performed for the force data based on a pilot study with seven subjects in each group, adopting an alpha level of 0.05 and a power of 80%, resulting in a minimum of 20 participants in each group in order to compare differences. For EMG data, *a posteriori* calculation was performed to estimate the sample power.

Questionnaires

After subjects' acceptance, a non-blinded examiner applied a structured questionnaire in which the subjects were asked about clinical characteristics of migraine and/or self-reported neck pain such as: frequency (days/month); intensity (0-10 numerical pain scale); and time period (years) with migraine and/or neck pain.

Procedures

The sequence of data collection for all subjects was: (1) EMG sensors positioning; (2) craniocervical flexion test; and (3) force measurement from maximal isometric voluntary contractions (MIVC) of neck muscles. This sequence was not randomized to avoid the influence of pain and/or fatigue promoted by MIVC from the results of other tests and to assess subjects in a progressive level of task difficulty. These procedures were carried out by a blinded examiner.

Surface electromyography of neck muscles was recorded using the Trigno^{TM} Wireless System (Delsys, Inc.; Boston, MA). The subjects' skin was properly cleaned with alcohol and tricotomized; then sensors were firmly affixed to the subjects' skin with adhesive tape. Sensors were always placed by the same examiner bilaterally at the sternal head of the sternocleidomastoid muscle (SCM), one-third distal to the muscle belly,[69] the anterior scalene muscles (AS), the third portion of the muscle belly parallel to the clavicular head of the SCM,[69] the splenius capitis muscles (SPLEN) (the palpable portion between the upper trapezius and the SCM, located between 6-8cm lateral of the median line at level of C4[70]), and the upper trapezius (UT) muscles, with a mean distance between the acromion and the spinal process of C7.[71]

The EMG sensor is comprised of four parallel bars of 99%Ag, two active electrodes, and two stabilizing references, with the following specification: a contact area of 50mm^2 (5x1

mm with an inter electrode distance of 10mm); a gain of 1000 V/V; and a common-mode rejection ratio >80dB. The overall system presents a maximal latency between electrodes of <500μs, a delay of 48ms from input to analog output, baseline noise <4.5uV pk-pk, a 16-bit resolution, and a sample rate of 4000Hz.

Myoelectrical signals were acquired by the software EMGworks acquisition (Delsys Inc. Boston, MA), amplified (gain=300), and sampled at 4000 Hz per channel.

Craniocervical flexion test (Article 2)

The craniocervical flexion test (CCFT) is applied to examine the subject's ability to maintain a low-load craniocervical flexion under five difference pressure targets, ranging from 22-30mmHg, without flexion of the mid- and lower cervical spine. It investigates the action of deep cervical muscles, specifically the longus colli in synergy with the longus capitis, responsible for providing adequate support and stability of the cervical segment as well as producing a flattening of the normal cervical spine lordosis.[72] Signs of inappropriate performance such as head retraction, head lift, or inability to relax after contractions are considered to be compensation strategies.[51]

As described in Article 2, subjects were assessed in supine position with a pressure feedback unit (Stabilizer; Chattanooga Group, Hixon, TN) placed behind the neck (Figure 1). CCFT started with a stable baseline pressure of 20 mm Hg and subjects were asked to perform a gentle head-nodding at craniocervical flexion to achieved 22 mmHg. Subsequently the test progressed up to 30mmHg with an increment of 2mmHg at each stage. All subjects were familiarized with the CCFT by holding each stage for 2sec and they were instructed to avoid compensation strategies. After a rest period of 1 minute, subjects performed craniocervical flexion and held each level for 10sec with a 30-sec rest period between stages. At this holding phase, electromyography (EMG) of the neck muscles was acquired. All subjects performed all CCFT stages and compensations were not controlled.

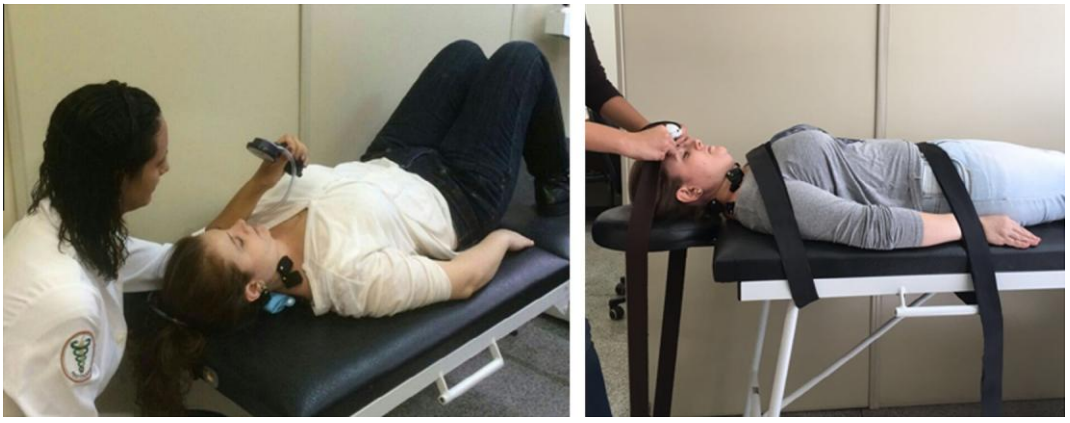

Figure 1. Illustration of the cranio-cervical flexion test performance and maximal voluntary contraction with the acquisition of neck muscles electromyography (reproduction of the Figure 1 of article 2 included in the results section).

Raw EMG signals from superficial cervical flexors (SCM and anterior scalene) and extensors (splenius capitis and upper trapezius) were processed by a customized MATLAB code (The Mathworks^{TM}; Natick, MA, USA). Data were band-filtered at 20-500Hz (fourth-order Butterworth), and Root Mean Square (RMS) were calculated from a 5-sec window. RMS for flexors and extensors during all CCFT stages were normalized and expressed in percentages of RMS from a 2-sec trial maximal voluntary isometric contraction in flexion and extension direction respectively.

Force measurement (Article 3)

Force production by MIVC was measured by a blinded examiner using a customized hand-held dynamometer (HHD) (Model 01163; Lafayette Instrument Company, Lafayette, Ind., USA) with a measurement range of 0-136.1kg and an accuracy of 1% over full scale. The HHD was connected to a non-elastic belt to avoid external force records provided by the examiner's hand during stabilization.[73,74]

The subjects' position during force measurement is detailed in Article 1 and represented here at Figure 2. One sub-maximal contraction was performed to familiarize subjects with the task. Data were obtained from three repetitions of cervical flexion, extension, and bilateral lateral flexion MIVC lasting 3sec per repetition, with a 15-sec rest period between repetitions and 2min between contractions. The order of assessment was randomly chosen by drawing. The examiner provided standardized verbal encouragement

during contraction recording. For each trial, peak force, time to produce the peak force, and neck and head-referred pain intensities were registered.

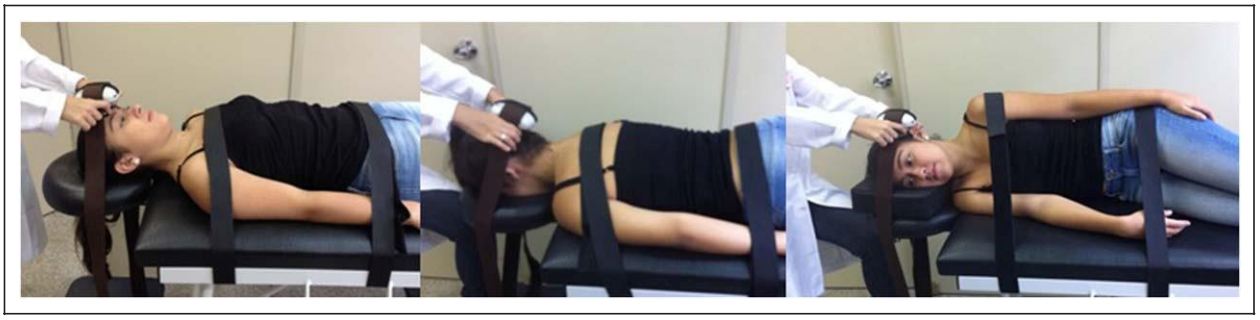

Figure 2. Position for strength measurements with an adapted hand-held dynamometer for maximal isometric contractions at cervical flexion, cervical extension, and cervical lateral flexion directions (reproduction of the Figure 1 of the article 3 included in the results section).

As peak force was recorded in kgf, we converted it into N and normalized it in terms of the subject's body mass. The conversion formula used was: (HHD reading [kgf]* 9.81/body mass [Kg]). Maximal value among three repetitions for each movement was used for statistical analysis.

In Article 3, we also analyzed the cervical muscle co-activation during MIVC based on antagonist-normalized EMG data. EMG raw signals were band-filtered at 20-500 Hz (fourth-order Butterworth) and the RMS were calculated from a 2-sec window of each MIVC repetition. Data were analyzed using EMGworks Analysis software (Delsys Inc.). Antagonist muscle activity was normalized by its maximal RMS value, as obtained during the record of muscle activity when acting as agonist. For instance, SCM antagonist activity in neck extension was assessed by normalizing RMS during cervical extension by its RMS during cervical flexion. All EMG data were calculated from the same trial in which peak force was produced. The mean of both sides, right and left, was considered in the main analysis.

Median Frequency and Slope (Article 4)

Data were analyzed using a customized MATLAB code (The Mathworks^{TM}; Natick, MA, USA). EMG raw signals were band-filtered at 20-500Hz (fourth-order Butterworth). Time domain analysis was performed in a 2-sec window and amplitude, represented by the average root-mean-square (RMS), was calculated. The highest EMG value of each MIVC

(peak) was used to normalize EMG data from each trial. MDF is a spectral index derived from raw signals by the fast Fourier transform algorithm and represents the frequency that divides the power spectrum into two equal areas.[75] It was calculated using a moving window of 0.375sec with an overlapping rate of 50%. Fatigue index (i.e., MDF slope) was determined using a linear best-fit analysis by the identification of the angular coefficient. Negative values indicate that MDF is decreasing in function of time, shifting the power spectrum density curve to lower rates of frequency. This shifting is representative of electromyographic fatigue.[76,77]

2.3 Study 3 (Articles 5 and 6)

Study design and ethical aspects

This cross-sectional study and the methods applied to assessment were approved by the *Comité Ético de Investigación Clínica de la Fundación Jimenez Diaz* (process number 07/14) (Attachment 3) and by the *Comité de Ética de la Investigación de la Universidad Rey Juan Carlos* (process number: 23/2014) (Attachment 4). All subjects signed the informed consent form.

Sample

Women with migraine, aged between 18 and 60 years old, were recruited from the Neurology Department Hospital Rey Juan Carlos, Madrid (Spain) from November 2014 to October 2015. Patients were diagnosed by an experienced neurologist following the beta version of the third edition of the International Headache Society criteria.[1] Exclusion criteria were: (1) other concomitant primary or secondary headache; (2) medication overuse headache; (3) history of cervical or head trauma (i.e., whiplash); (4) pregnancy; (5) history of cervical herniated disk or cervical osteoarthritis in medical records; (6) any systemic degenerative disease (e.g., rheumatoid arthritis, lupus erythematous); (7) diagnosis of fibromyalgia syndrome; (8) anesthetic block in the past three months; or (9) receiving physical therapy intervention in the head and neck the previous six months. A careful clinical examination of each participant was conducted to determine inclusion and exclusion criteria.

From 122 eligible subjects with migraine who accepted to participate, 54 were excluded for the following reasons: co-morbid headaches (n=19); receiving anesthetic block

(n=8), botulinium toxin (n=5) or physical therapy (n=6); diagnosis of fibromyalgia (n=6); neck/head trauma (n=3); visual disturbance (n=4); or dizziness (n=3).

Questionnaires

Structured form was applied by a non-blinded examiner to assess the clinical characteristics of migraine and/or self-reported neck pain such as: frequency (days/month); intensity (0-10 on the numerical pain scale); and time period (years) with migraine and/or neck pain.

Procedures

Head and neck posture (Article 5)

To avoid the influence of fatigue or pain due to manual palpation, a photograph was taken first. The head/neck posture was evaluated by a profile photograph of the cervical spine. An experimental procedure followed standardized anatomical (occiptal bone, spinous processes of the fourth and seventh cervical vertebrae) and vertical references (metal plumb line), as well as the distance and height of the camera (4m from the subject and adjusted according to the subject's height).[41,78,79]. All photographs were obtained by the same technician using a digital camera with a lens of 23mm (Samsung Lens WB350F®). Volunteers were photographed in standing upright and sitting positions without shoes. Instructions were given to maintain a comfortable position.[47,80]

Photographs were analyzed using CorelDraw-X7® software. Head posture was assessed by calculating the cranio-vertebral angle (CV) and neck posture by determining the cervical lordosis angle (Figure 3).[47,81,82]

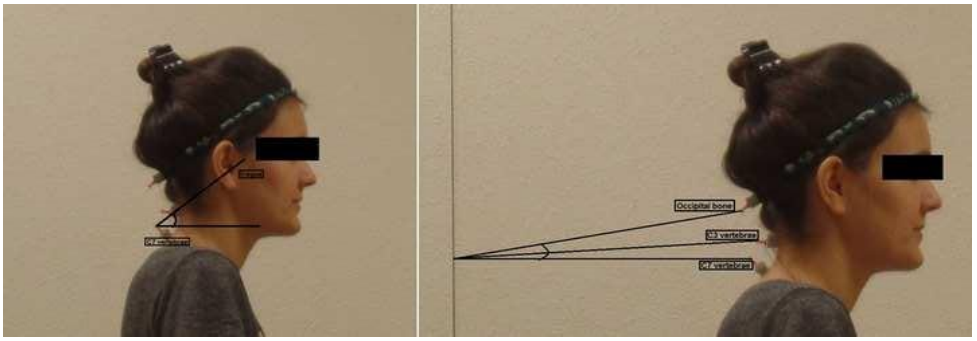

Figure 3: Assessment of the cranio-vertebral (left) and cervical lordosis (right) angles (reproduction of Figure 1of the article 6 included in the results section).

Cranio-cervical flexion test (Articles 5 and 6)

The CCFT performance followed the same protocol described for Study 2. To acquire the myoelectrical signal, each stage target was maintained for 10sec and repeated two times with a 30-sec resting interval between them.

Electromyography acquisition and processing (Articles 5 and 6)

Bipolar surface electrodes were positioned 22mm apart (Ambu®-Blue Sensor N-50-K/25) after gentle skin abrasion using abrasive paste and shaving when necessary. Electrode placement was the same as described for Study 2, except for the splenius capitis.[83] A grounding electrode was placed around the subject's wrist. Myoelectric signals were acquired and amplified by 5000 (EMG16, 16-channel amplifier, LISiN-OT Bioelettronica®; Torino, Italy), filtered (−3dB bandwidth, 10-450 Hz), sampled at 2048 Hz, and converted to 12-bit digital samples. Raw signals were band-filtered at 20-400Hz (fourth-order Butterworth), and the average RMS was calculated from each 10-sec contraction by a customized MATLAB code (The Mathworks™, Natick, MA, USA). Electrical activity was normalized by the maximum RMS during the reference voluntary contraction and expressed as a percentage. Reference activities consisted of head lift for superficial neck flexors, and head extension with manual resistance for neck extensors, because submaximal normalization has demonstrated that this reduces variability and is considered to be more acceptable in patients with pain than maximal contraction normalization procedure.[84] Both contractions were performed with participants in a supine position, sustained for 10sec and repeated two times after the CCFT

performance. The average from two repetitions of left and right neck muscle RMS values was used in the analysis.

Trigger points (TrP) assessment (Article 6)

The SCM, SC, and UT were bilaterally assessed in order to identify TrP. TrP diagnosis was performed according to the following criteria:[85] (1) presence of a palpable taut band in the muscle; (2) presence of a painful spot in the taut band; (3) local twitch response on snapping palpation of the taut band; and (4) reproduction of referred pain during manual examination. TrPs were considered active when the pain was recognized as a familiar pain. Patients were classified as having active TrPs when they had TrPs reproducing their migraine attack in at least one muscle, either left or right side.

3 Results

3.1 Article 1- Published at Headache 2014;54:1203-1210

Neck Pain Disability Is Related to the Frequency of Migraine Attacks: A Cross-Sectional Study

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Background.—Migraine and neck pain can be critical causes of disability. The contribution of neck pain for the overall disability of individuals with migraine remains unknown.

Objective.—To contrast the disability experienced by individuals with episodic and chronic migraine with and without neck pain as captured by the Neck Disability Index.

Methods.—Disability due to neck pain was assessed using the Neck Disability Index in individuals with episodic or chronic migraine seen at a university-based headache center. Neck disability was defined as mild (score ranging from 5 to 14 points), moderate (15-24 points), severe (25-34 points) or complete (35 points or higher). To compare differences between groups, a chi-square test was applied. Log-binomial logistic regression was used to estimate disability as a function of headache status after adjustments for age, time since migraine onset, and headache intensity.

Results.—Sample consisted of 169 individuals, 104 with episodic migraine and 65 with chronic migraine. Any disability due to neck pain happened in 69% of those with episodic migraine, relative to 92% in chronic migraine (*P* < .001). Individuals with chronic migraine were at a significantly increased risk to have mild (RR = 2.5; CI 95% 1.1-6.1), moderate (RR = 3.7; CI 95% 1.5-8.8) and severe (RR = 5.1; CI 95%2.1-11.9) cervical disability relative to those with episodic migraine. Relative risks remained

significant after adjustments. Time since episodic or chronic migraine onset significantly influenced the model (*P* = .035), but age and headache intensity did not (*P* = .27; *P* = .46).

Conclusion.—Neck pain significantly adds to the overall disability of individuals with episodic and chronic migraine. **Key words: cervical pain, chronic migraine, migraine, Neck Disability Index, relative risk**

Abbreviations: CI confidence interval, CM chronic migraine, EM episodic migraine, NDI Neck Disability Index, RR relative risk

(*Headache 2*014;54:1203-1210) doi: 10.1111/head.12393

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Accepted for publication March 14, 2014.
Conflict of Interest: None.

This research received a grant from the São Paulo Research Foundation (FAPESP).

Migraine may be conceptualized as a chronic disorder with episodic attacks in which for a subgroup of individuals it eventually evolves into a stage where they have headaches on more days than not, a condition called chronic migraine (CM).[1,2] CM ranks among the eight most burdensome conditions according to the Global Burden of Disease of the World Health Organization.[3]

The prevalence of neck pain ranges from 30% to 50% in the general population.[4] Similar to migraine, prevalence of cervical pain peaks in middle life and women are disproportionally affected.[1,4]

An association between migraine and cervical spine disorders has been suggested. Relative to individuals without migraine, those with migraine are more likely to self-report neck pain, to have more cervical trigger points, and to report tenderness on the cervical muscles.[5-11] Migraineurs are also more likely to have decreased cervical range of motion and decreased pressure pain threshold on the cervical muscles.[12-14] It has been speculated that the trigeminal-cervical anastomosis provides a path for mutual interaction via the convergence of cervical and trigeminal nociceptive afferents in the trigeminocervical complex.[15,16]

Neck pain may confound the migraine diagnosis and affect treatment choices.[17] Furthermore, neck pain seems to be comorbid to CM[7] and is a significant predictor of headache-related disability regardless of other headache characteristics, such as frequency and severity.[18]

Migraine-related disability and neck pain prevalence are well defined, but the contribution of neck pain to the overall disability of migraineurs remains to be explored. Accordingly, herein we aimed to contrast the disability experienced by individuals with episodic migraine (EM) and CM with and without neck pain. We hypothesized that disability due to neck pain is prevalent in migraine patients and its severity is influenced by the frequency of migraine attacks.

METHODS

Participants were selected among the patients who went to a neurologist appointment at a university-based headache center in Ribeirao Preto, Brazil, from August 2010 to September 2012. Sample consisted of women with ages ranging from 18 to 65 years, and with EM or CM. Headache diagnoses were assigned by neurologists according to the Second Edition of the International Classification of Headache Disorder criteria.[2] Herein we call EM those with migraine and less than 15 days of headache per month. Exclusion criteria were the presence of concomitant headache diagnosis (including tension-type headaches), history of cervical trauma and/or self-report of cervical diseases. Patients agreeing to participate and fulfilling the criteria

were enrolled. The study was approved by our University Ethics Committee on Research (process n 14100/2010).

At the same day of the neurologist appointment, volunteers signed informed consent forms and were interviewed by a non-blinded examiner about the headache characteristics, such as frequency, time of migraine onset, and headache intensity (using a numerical scale ranging from 0 to 10). This interview was done in a cubicle, immediately after leaving the neurology office. Participants were then redirected to another office where a second examiner, blinded for the diagnosis, applied the validated Brazilian version of the Neck Disability Index (NDI).[19]

The NDI is a widely used questionnaire that was designed to assess disability due to neck pain.[20] It consists of 10 items measuring the influence of neck pain on daily activities. Individual items are scored and the total score can range from 0 to 50. Neck disability is classified as follows, as a function of NDI score: 0-4 = absence of disability; 5-14 = mild;15-24 = moderate; 25-34 = severe; 35 or higher = complete.[21] The NDI has excellent psychometric proper- ties, including internal consistency and construct validity.[20,21]

Statistical Methods.— The sample size was calculated to yield a 90% of power for detecting a 10% difference at the 5% significance. The minimum sample size was 60 participants per group.

Descriptive analyses and frequency counts were used to characterize the sample and summarize headache characteristics and the NDI scores. For a better description of the NDI items data, we accounted for two situations: (1) the frequency of positive answer at each NDI item, in order to identify individual item contribution for disability, and (2) the mean items scores stratified by the presence of neck pain at the time of the assessment (one or more points at question number 1 of the NDI) to verify the additional influence of the neck pain at overall disability.

Statistical analysis was performed using SAS and 95% confidence intervals (95% CI) and two-tailed *P* values were calculated. When data had normal distribution, means were compared using the Student's *t*-test for independent samples. To test the correlation between the NDI scores and frequency of headache attacks in univariate analyses, we applied the Pearson's correlation coefficient between frequency of attacks (days/month) and NDI scores.

Correlation was classified as weak (<0.30), moderate (between 0.30 and 0.70), or strong (>0.70).[22] Missing data were excluded from analysis.

In multivariate analyses, log-binomial logistic regression was used to estimate disability as a function of headache status after adjustments for age, time since migraine onset, and headache intensity. The chi- square test was applied to compare the prevalence of disability and to compare the positive answers for each NDI item between EM and CM.

RESULTS

All volunteers agreeing to participate were interviewed (n = 519). Of them, 169 met the inclusion criteria; 104 had EM (mean age = 36 years, SD = 10.7) and 65 had CM (mean age = 38 years, SD = 10.2) (P = .25) (Fig. 1). Mean headache severity was slightly higher in EM relative to CM (EM = 8, SD = 1.5; CM = 8.5, SD = 1.5; P = .05). Individuals with EM had a mean of seven headache days per month (SD = 3.8) vs 24 in the CM group (SD = 6.0) (P < .001). Individuals with EM had more recent onset of disease (14 years, SD = 8.8) vs CM (19 years, SD = 11.9, P = .010) (Table 1). We emphasize that, for CM, we refer to onset of CM, not of any migraine.

Neck disability was reported by 69% of those with EM and 92% of those with CM. NDI scores were significantly higher in CM (mean = 16.2; SD = 8.4) relative to EM (mean = 10.5; SD = 8.5, P < .001). Of individuals with EM, 43% had mild disability, 19% had moderate disability, 7% had severe disability, and 1% was completely disabled. For CM, values were 35%, 31%, 23%, and 3%. The prevalence rates of severe and complete disability were significantly higher in CM compared with EM (respectively, P = .004 and P = .003).

When headache frequency was treated as a continuous variable (instead of dichotomized in EM and CM), moderate positive correlation was found between severity of neck disability and migraine frequency (r = 0.32; CI 95% 0.19-0.46) (P < .001) (Fig. 2).

Table 1.—Mean and Standard Deviation (SD) of the Age and Headache Characteristics for Episodic (EM) and Chronic Migraine (CM)

	EM (n = 104)		CM (n = 65)		P Value
	Mean	SD	Mean	SD	
Age (years)	36.8	10.7	38.7	10.2	.25
Frequency (day/month)	7.3	3.8	24.2	6.0	<.001
Time since headache onset (years)	14.9	8.8	19.4	11.9	.010
Headache intensity (numerical pain scale) †	8.0	1.5	8.5	1.5	.050

†The sample size considered for headache intensity summaries were 85 for EM and 55 for CM because of missing data.

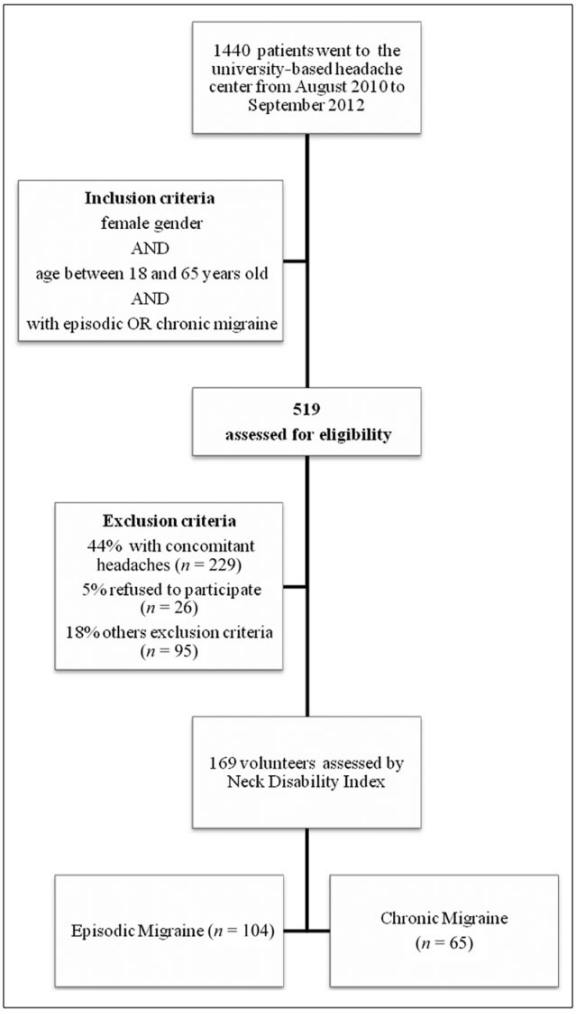

Fig 1.—Flow diagram of the sample selection.

Individuals with CM were at a significantly increased risk of having mild (RR = 2.5; CI 95% 1.1-6.1), moderate (RR = 3.7; CI 95% 1.5-8.8) and severe (RR = 5.1; CI 95% 2.1-11.9) neck disability relative to EM (Table 2). Considering that age, overall perception of pain, and presence of chronic pain may influence NDI scores, adjustments accounted for these variables. Relative risks remained significant after adjustments: mild (RR = 1.4; CI 95% 1.01-2.1), moderate (RR = 1.6; CI 95% 1.1-2.3), and severe disabilities (RR = 1.6, CI 95% 1.1-2.4). Time since migraine status onset significantly influenced the model (P = .035), but age and headache intensity did not (P = .27; P = .46).

Table 2.—Neck Disability Index (NDI) Classification and Relative Risk (RR) Estimation in Chronic Migraine (CM) and Episodic Migraine (EM)

	EM (n = 104)		CM (n = 65)			
NDI Classification†	*n*	%	*n*	%	RR	CI 95%
None	32	31*	5	8	Ref.	Ref.
Mild	44	42	23	35	2.5	(1.05-6.1)
Moderate	20	19	20	31	3.7	(1.5-8.8)
Severe	7	7	15	23*	5.05	(2.1-11.9)

*P < .05.
†The *complete* subgroup was not considered because it only has three subjects.

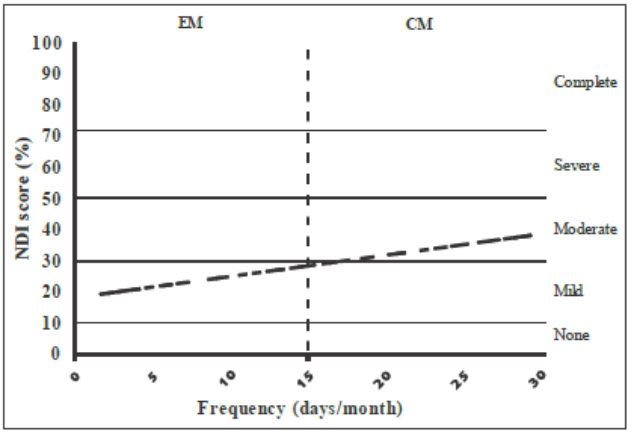

Fig 2.—Correlation between the frequency of attacks (days/month) and Neck Disability Index (NDI) scores (percentage). The figure is divided according to migraine groups (CM = chronic migraine; EM = episodic migraine) and NDI classification.

Relative to individuals with EM, those with CM had significantly more difficulty to lift ($P < .001$), to read ($P = .001$), to concentrate ($P = .001$), to work ($P = .002$), to sleep ($P < .001$), to enjoy recreation time ($P = .010$) (Fig. 3).

Figure 4 displays the magnitude of impairment for the several items. It becomes evident that, after stratifying for presence of neck pain, individuals with EM and CM (with cervical pain) have strikingly similar item and overall disabilities.

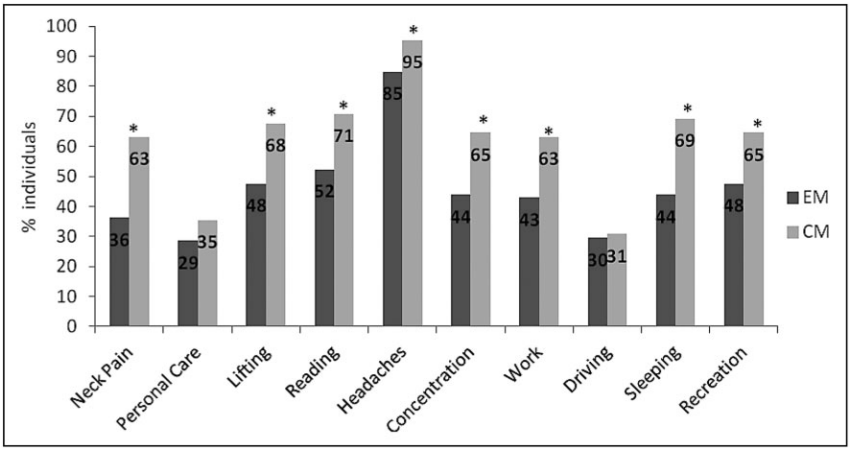

Fig 3.—Frequency of positive answer for neck pain-related disability on Neck Disability Index (NDI) items. *Significant difference. CM = chronic migraine; EM = episodic migraine.

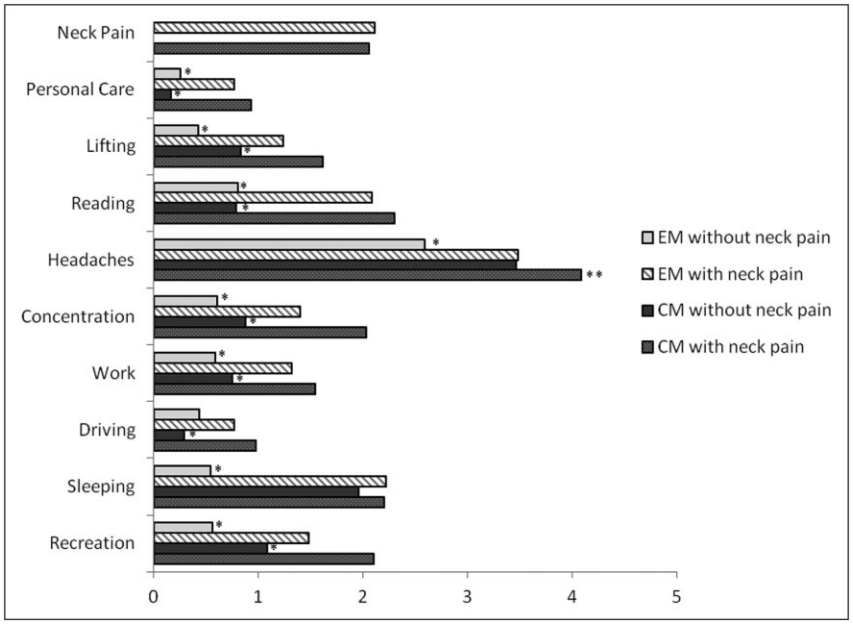

Fig 4.—Neck Disability Index scores mean for each activity stratified by the presence of neck pain at the moment of the assessment. CM = chronic migraine; EM = episodic migraine. *Significant difference between EM/CM with neck pain vs EM/CM without neck pain; **significant difference between CM with neck pain vs EM with neck pain.

DISCUSSION

Our hypothesis was partially confirmed. We found that disability due to neck pain is highly prevalent in EM and CM. Furthermore, frequency of migraine attacks correlated with NDI scores. Different than we hypothesized, however, we found that though individuals with CM are more likely to have disability due to neck pain than EM, after stratifying by the presence of cervical pain, the magnitude of disability at each activity is strikingly similar between groups. In other words, neck pain is the driver of the disability. Individuals with CM are more likely to have neck pain than individuals with EM, but in the presence of pain the disability is similar. To the best of our knowledge, similar data have not been reported elsewhere.

As expected, time since migraine onset was associated with NDI scores. Individuals with migraine are more likely to report neck pain relative to individuals without migraine, and this may be explained by the convergent afferent inputs of C1 and C2 into the trigeminocervical complex. Repetitive stimulation of the trigeminocervical complex leads to trigeminal sensitization and deficient central modulation of pain.[23-25] Consequently, disability due to neck pain not surprisingly correlates with migraine frequency and with time since migraine onset.

The analysis of NDI individual scores suggest that most impaired activities were those requiring sustained stabilization and alignment of the cervical segment in order to maintain proper posture. It may be speculated that the disability for these specific tasks may be a functional repercussion of the altered craniocervical posture of migraine patients[26] associated with reduced cervical spine stability due to the secondary changes in muscle tone in patients with neck pain.[27]

It is relatively difficult to contextualize our data because of the scarcity of studies focusing on disability due to neck pain in migraine patients. For the prevalence of cervical pain, we found rates that were similar to those reported by Calhoun et al.[7] It has also been reported that cervical pain and migraine attack frequency are positively correlated,[18] and that pain is a migraine trigger or a premonitory migraine symptom in some patients.[28]

Although comparative data for CM are not available, the NDI scores found by us have similar magnitude of what has been found after whiplash injuries,[29] a very disabling neck condition.

Our findings have clinical importance. The understanding of the contribution of neck pain to migraine- related disability is useful in developing educational interventions for migraineurs focusing on daily posture and self-management of pain. We do not suggest that clinical decisions should be made based on single NDI items, but neck-specific questionnaires can provide a broader and deeper understanding of the impact of neck pain.[20] A subgroup of patients may indeed benefit from physical therapy aiming to decrease the cervical pain.

Perhaps the most important findings of our study were that individuals with CM are more likely to report neck disability (mainly the most disabling forms) than those with EM. However, the magnitude of disability due to the neck pain is very similar in EM and CM at most items. Because neck pain contributes to the NDI score, and because prevalence of neck pain is higher in CM relative to EM, total NDI scores reflect this fact.

Our study has limitations. First, individual NDI items capture conditions that are not only specific to neck pain, but also to migraine headaches, such as sleep disorders.[30] Furthermore, in individuals with migraine and neck pain, it is difficult to disentangle the individual contribution of each condition (neck pain or migraine). Nonetheless, contrast after stratification by the presence of neck pain and after adjustments allow us to state that neck pain significantly is a powerful contributor to the overall disability of individuals with EM and CM. Second, we cannot discuss causality, only association, since the study was cross-sectional. Furthermore, shared risk factors to both migraine and neck pain (eg, other chronic pain syndromes, depression, trigeminal or cervical allodynia) were not assessed, and we cannot rule out the possibility of spurious association. Also, our study contrasted two migraine stages, and we lack a contemporaneous control group (individuals without headache or with tension-type headache). Finally, the prevalence of the neck disability in both groups could represent an overestimation because sample was enrolled from a headache clinic, where patients are more severely affected than in the population. Therefore, the generalizability of our findings is restricted to patients with similar characteristics.

CONCLUSION

Disability due to neck pain is highly prevalent in individuals with episodic and chronic migraine. Individuals with CM are more likely to have any disability, as well as severe disability, due to cervical problems relative to those with EM, and the difference is explained by the increased prevalence of neck pain in CM relative to EM.

Acknowledgments: The authors acknowledge the Headache and Craniofacial Disorders Ambulatory for the contribution, especially Professor José Geraldo Speciali for the opportunity of a multidisciplinary approach and the São Paulo Research Foundation (FAPESP) for the financial support.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the Online version of this article at the publisher's web-site.

Appendix S1.—Neck Disability Index

3.2 Article 2- Published at J Electromyogr Kinesiol. 2016;30:66-72

Patients with chronic, but not episodic, migraine display altered activity of their neck extensor muscles

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A r t i c l e i n f o

Article history:

Received 4 March 2016

Received in revised form 3 June 2016

Accepted 8 June 2016

http://dx.doi.org/10.1016/j.jelekin.2016.06.003

Keywords: Cervical spine, Cranio-cervical flexion test, Migraine, Pain, Surface electromyography.

Abstract

The current study aimed to investigate differences in activity of neck flexor and extensor muscles in women with migraine considering the chronicity of their condition. Thirty-one subjects with episodic migraine, 21 with chronic migraine and 31 healthy controls participated. Surface electromyography signals were recorded bilaterally from the sternocleidomastoid, anterior scalene, splenius capitis and upper trapezius muscles as

subjects performed 5 stages of cranio-cervical flexion (CCF), representing a progressive increase in range of CCF motion. Comparison of normalized root-mean-square among groups was conducted with 3x5 ANCOVA with task level as the within-subject variable, group as the between-subject variable, and the presence of neck pain and disability as covariates. The group with chronic migraine exhibited increased activity of their extensor muscles compared to the control and episodic migraine groups (splenius capitis: $F = 3.149$, $P = 0.045$; upper trapezius: $F = 3.369$, $P = 0.041$). No significant between-group differences were found for the superficial neck flexors (sternocleidomastoid: $F = 1.161$, $P = 0.320$; anterior scalene: $F = 0.135$, $P = 0.874$). In conclusion, women with chronic migraine exhibit increased activity of their superficial neck extensor muscles when acting as antagonists during low-load isometric CCF contractions in comparison to non-headache subjects.

1. Introduction

Migraine is a primary headache that affects 15% of the general population (Stovner et al., 2014) and about 2.5% can progress to the chronic form (Bigal et al., 2008). It is associated with a primary brain dysfunction consisting of deficient regulation of excitatory-inhibitory balance resulting in sensitization of trigemino-vascular pain pathways (Vecchia and Pietrobon, 2012). Sensitization may also result in facilitation of pain, particularly at the cranio- cervical region due to sensitization of the trigemino-cervical nucleus caudalis (Calhoun et al., 2010; Plesh et al., 2012). Patients with migraine may exhibit neck pain and hypersensitivity to mechanical stimuli (Ashina et al., 2015; Fernández-de-las-Peñas et al., 2010). In fact, the presence of neck pain is a predictor of more severe migraine-related disability (Ford et al., 2008) and reduced efficacy of medical treatment (Calhoun et al., 2011; Calhoun and Ford, 2014). Further, more severe neck-related disability is associated with migraine chronification (Florencio et al., 2014).

The comorbidity of migraine and cervical pain may be bidirectional. A subgroup of subjects with migraine may develop a secondary cervical musculoskeletal dysfunction. In association with migraine, neck pain is reported as a symptom that can be present before, during or after a migraine attack. However, neck pain cannot exclusively be attributed to peripheral structures; the dysfunctional modulation of pain may be the potential mechanism underlying the concurrence of neck pain in migraine (Ashina et al., 2015; Calhoun et al., 2010). The opposite may be true as well. Chronic dysfunction of the peripheral structures could, in turn, sensitize pain pathways and predispose to a high frequency of migraine attacks.

Prolonged experience of pain within the cervical region can promote altered patterns of neck muscle activation. The motor adaptations can contribute to promotion or perpetuation of signs and symptoms of neck muscle dysfunctions (Sterling et al.,2001). This knowledge suggests that migraineurs with neck pain may also display altered patterns of neuromuscular activation. However, few studies have investigated neuromuscular control of the neck muscles in people with migraine. Two studies compared tension-type, migraine, cervicogenic headache and healthy controls during the performance of the cranio-cervical flexion test (CCFT) (Jull et al., 2007; Zito et al., 2006). No differences in activation of superficial neck flexors between migraine and controls were observed. CCFT is a low-load test used to evaluate neuromuscular control of the deep neck flexors (i.e., longus colli and longus capitis) function (Falla et al., 2003a,b, 2006; Jull et al.,2008). Poor performance is identified as increased compensatory activity of sternocleidomastoid (SCM) and anterior scalene (AS)

muscles when compared to controls (Falla, 2004; Jull et al., 2008). Such increased activity of the superficial neck muscles is a common observation in individuals with primary cervical disorders regardless of the cause of their pain (Falla, 2004; Jul et al., 2007, 2004; O'Leary et al., 2007).

However, in previous studies, no distinction between episodic and chronic migraine was made, and the activity of other muscles, i.e., neck extensor muscles, was not measured (Jull et al., 2007; Zito et al., 2006). Evidence suggests that neck muscle co-activation may be an adaptation mechanism related to headaches (Fernández-de-las-Peñas et al., 2010; Oksanen et al., 2008).

This study aimed to gain a deeper perspective of changes in neuromuscular control of the cervical spine in people with migraine considering the antagonist activity and chronicity of migraine to provide better directions for treatment. Accordingly, the objective of this study was to investigate differences in activation of superficial neck flexor and extensor muscles during the CCFT in migraine patients considering the chronicity of the condition. We hypothesized that patients with migraine, especially those with more frequent migraine attacks, would exhibit greater activity of their superficial neck flexors and extensors during the CCFT compared to headache-free participants.

2. Methods

2.1. Participants

Women aged between 18 and 55 years-old with migraine were recruited from a university-based hospital between January-October 2014. They were invited to participate in this cross-sectional study following an appointment with an experienced neurologist. Migraine diagnosis followed the 3rd edition of International Headache Society criteria (Headache Classification Committee, 2013). Patients who presents more than 15 days of headache per month with at least 8 with migraine characteristics is diagnosed as chronic migraine; and those with <15 attacks per month are included in the episodic group (Headache Classification Committee, 2013). Exclusion criteria included: 1, other primary/secondary headache; 2, medication overuse headache; 3, history of neck/head trauma; 4, pregnancy; 5, history of cervical herniated disk or cervical osteoarthritis; 6, any systemic degenerative disease, e.g., rheumatoid arthritis, lupus erythematous; 7, fibromyalgia; or, 8, anesthetic blocks within the past month. A careful clinical examination of each participant was

conducted to determine inclusion and exclusion criteria and all medical history was checked from hospital records.

A group of healthy individuals without headache, similar in age to the migraine group, was also included. Inclusion criteria were no headache history or only occasional non-severe headaches over the past year without need of medical treatment. Exclusion criteria for the control group were the same as the migraine group. All subjects signed the informed consent form before their inclusion in the study. The local Ethics Committee approved the study design (process 16692/2012).

2.2. Clinical data

Demographic and clinical data were collected during an interview and included headache frequency (days/month), pain intensity (numerical pain rate scale [NPRS], 0–10), history (years) of disease, and self-report neck pain, including report of frequency, intensity and years with neck pain. In addition, neck-related disability during daily activities was assessed with the Neck Disability Index (NDI) questionnaire (Vernon and Mior, 1991). Subjects were classified according to their NDI score as no disability (0–4 points), mild disability (5–14 points), moderate disability (15–24 points), severe disability (25–35 points) or complete disability (P36 points) (Vernon, 2008).

2.3. Instrumentation

The data were collected using the Trigno TM Wireless System (20–450 Hz; CMRR of 80 dB, input impedance exceeding 1000 X, Delsys Inc. Boston, MA) with 16 channels. Trigno sensors (50 mm2 area; USA patent 6480731, 6238338; European Patent EP 1070479) are composed by 4 parallel bar (Ag-AgCl), two references and two active surface electrodes with an inter-electrode distance of 10 mm. The skin was shaved (if necessary) and cleaned with isopropyl alcohol. Sensors were firmly fixed with proper adhesive sensor interface, positioning the pair of active differential simple electrodes parallel to the muscles fibers, bilaterally over: 1. the sternal head of SCM, over the distal 1/3 of the muscle belly (Falla et al., 2002); 2. AS: over the muscle belly parallel to the clavicular head of the SCM muscle (Falla et al., 2002); 3. splenius capitis (SPLEN): palpable portion between the upper trapezius and SCM located between 6 and 8 cm lateral of median line at level of C4 (Sommerich et al., 2000); 4. upper trapezius (UT): midpoint between C7 spinous process and acromial process

over the upper trapezius muscle belly (Mathiassen et al., 1995). Minimum distance between the centers of different electrodes was 20 mm and overall channel noise was <0.45 lV pk-pk. All sensors were positioned by the same trained examiner, blinded for group diagnosis.

Myoelectrical signals from SCM, AS, SPLEN and UT muscles were digitized, amplified (gain = 300) and sampled at 4 kHz with a 16-bit resolution A/D system (EMGworks acquisition; Delsys Inc. Boston, MA).

2.4. Experimental procedures

Clinical evaluation was held when all patients were headache- free. The CCFT was conducted by experienced clinicians with more than 5 years of experience in this assessment and blinded to the clinical condition of the subject.

The CCFT was performed with participants in supine. An inflatable air-filled pressure sensor (Stabilizer, Chattanooga South Pacific; USA) was placed behind the neck and inflated to 20 mmHg. Subjects were instructed to perform a gentle head-nodding action of cranio-cervical flexion over five incremental stages of increasing range (2 mmHg each stage), and each stage was maintained for 10 s. Signs of inappropriate performance such as head retraction, head lift, or difficulty relaxing after the contraction were considered incorrect strategies and discouraged during the familiarization phase of the test. Subjects performed two repetitions of 2 s at each stage to familiarize themselves with the task.

After the familiarization phase, a rest period of 1 min was permitted. Subjects then performed the CCFT holding each target level for 10 s with 30 s rest period between levels. During the holding phase, surface electromyography of selected neck flexors and extensors were acquired. All subjects performed all CCFT levels, and compensatory strategies were not controlled during the formal test (Fig. 1).

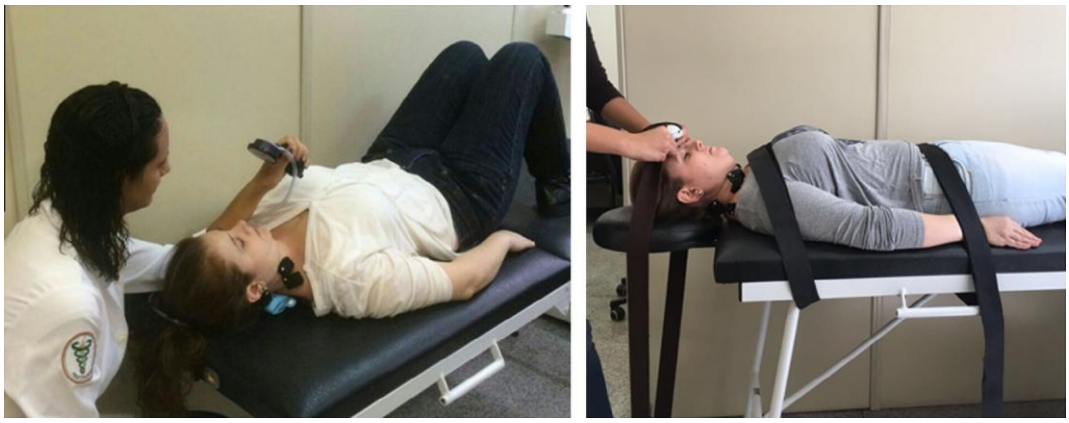

Fig. 1. Illustration of the cranio-cervical flexion test performance and maximal voluntary contraction with the acquisition of neck muscles electromyography.

Maximal isometric voluntary contractions in flexion and extension were performed to normalize electromyographic data. Subjects were first familiarized with the setting and trained to perform maximal voluntary effort with standard verbal encouragement. For cervical flexion, the volunteer was in supine with full-extended knees. Non elastic belts were fastened tightly at the level of the anterior superior iliac spine and crossing the chest over the sternum; an adapted hand-held dynamometer was positioned in the mean line of the frontal bone (Fig. 1). For head extension, volunteer was in prone, with arms alongside the body. Belts were fastened tightly crossing the posterior superior iliac spine and crossing the chest at T3 level. The hand-held dynamometer was placed at the mean line of the occipital protuberance. For both directions, head and neck started in neutral position relate to frontal, sagital and transverse plane and 3 repetitions of 3 s were performed with 15 s rest period between repetition and 2 min between flexion and extension (Florencio et al., 2015).

2.5. Data analysis

Customized MATLAB code (The MathworksTM, Natick, MA, USA) was used for data processing. EMG raw signals were band- filtered a 20–500 Hz (4th order Butterworth), and the average root-mean-square (RMS) was calculated for each channel. For signals from CCFT stages RMS was calculated from a central 5 s window. Neck flexor and extensor RMS values were normalized and expressed as a percentage of RMS recorded during the repetition of maximal isometric voluntary contraction that promotes the higher peak force, calculated from a 2 s window. The mean of both right and left sides for each muscle were considered in the analysis.

2.6. Statistical analysis

Data were analyzed with SPSS software version 20.0. Means and standard deviation (SD) were calculated. A one-way analysis of variance (ANOVA) was used to determine the differences among groups for demographic and clinical data. The comparison for the normalized RMS was conducted with a 3 5 analysis of co-variance (ANCOVA) with CCFT stage (22 mmHg, 24 mmHg, 26 mmHg, 28 mmHg, 30 mmHg) as the within-subject variable, group (chronic migraine, episodic migraine, controls) as between-subject variable, and the presence of self-reported neck pain and severity of neck-related disability (NDI classification) as co-variates. Pair-wise comparisons adopting Bonferroni procedure were administered as post-hoc test. Comparison between groups tested the hypothesis that groups differed in the level of their neck muscle activity, and comparison within subjects among CCFT stages evaluated whether muscle activity increased progressively with the levels of the test. Alpha was set at 0.05. Cohen's d was calculated to estimate the effect size of the differences among groups. Effect size was classified as small (0.2), moderate (0.5), and large (0.8). Moderate and large magnitudes of effect size were considered indicators of appropriate statistical power (Cohen, 1988; Page, 2014).

3. Results

3.1. Clinical features of the sample

From 116 eligible subjects with migraine, 14 did not accept to participate and another 50 were excluded. Reasons were co-morbid headaches (n = 19), receiving anesthetic block in the past three months (n = 16), reporting previous head/neck trauma (n = 8) or unavailability to attend the appointment (n = 7). Finally, 31 women with episodic migraine and 21 with chronic migraine participated. Further, 31 subjects without headache history were included. The presence of self-reported neck pain was significantly higher ($X^2 = 33.100$; $P < 0.001$) in the episodic (n = 24, 77%) and chronic (n = 19, 86%) migraine groups than the control group (n = 6, 19%). The intensity of neck pain ($F = 4.145$; $df = 2$; $P = 0.022$) and neck- related disability ($F = 33.945$; $df = 2$; $P < 0.001$) was also significantly greater in both migraine groups compared to controls. The frequency of neck pain was higher in chronic migraine than in healthy controls ($P < 0.001$). Moderate neck-related disability was the most prevalent classification at both, chronic and episodic migraine ($X2 = 32.108$; $P < 0.001$). No

significant differences were found for years with neck pain (F = 0.550; df = 2; P = 0.581). Table 1 shows the demographic and clinical data of each group.

3.2. Neck flexor activity

Fig. 2 presents the normalized RMS values for SCM and AS muscles during the five stages of the CCFT for each group. As can be observed, there was an increase in EMG amplitude of the SCM (F = 20.152; df = 1; P < 0.001) and AS (F = 14.660; df = 1; P < 0.001) with the progressive stages of the CCFT for all groups, without significant differences among groups (SCM: F = 1.161, df = 2, P = 0.320; AS: F = 0.135, df = 2; P = 0.874). The presence of neck pain (SCM: F = 0.615, df = 4, P = 0.653; AS: F = 0.286, df = 4, P = 0.752) or neck-related disability (SCM: F = 0.634, df = 4, P = 0.639; AS: F = 0.736, df = 4, P = 0.66) did not influence the results. Moderate effect sizes were observed for comparisons between chronic migraine and healthy controls in all CCFT stages for SCM (d: 0.5–0.6) and AS (d: 0.5–0.7) muscles. Both muscles presented small effect sizes when comparing episodic with chronic migraine (d: 0.1–0.4).

Table 1. Clinical and demographic characteristics of patients with episodic migraine, chronic migraine, and healthy controls.

	Episodic migraine (n = 31)		Chronic migraine (n = 31)		Healthy controls (n = 21)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	33	11.22	34	9.76	31	9.08
BMI (kg/cm2)	25.2	5.63	25.6	4.81	24.8	4.68
Neck pain [n (%)]*	24		19		6	
Time of onset (years)	7.6	6.30	5.4	5.89	5.4	6.90
Intensity (0–10)*	6.6	2.16	6.3	1.82	3.8	1.54
Frequency (days/month) †	10.7	9.95	18.5	11.27	5.2	5.67
Neck disability index	9.2	5.83	13.1	6.35	2.0	2.68
None n (%)	8		3		25	
Mild n (%)	15		9		6	
Moderate n (%)	8		9		0 (0%)	
Migraine						
Time of onset (years)	18.3	12.18	16.1	8.70		
Frequency	5.9	3.72	20.4	7.85		
Intensity (0–10)	7.6	1.80	8.0	2.73		

BMI: Body mass index.

* Significant differences between patients with migraine (both groups) and healthy controls ($P < 0.001$).

† Significant differences between patients with chronic migraine and healthy controls ($P < 0.001$).
Significant differences between patients with episodic and chronic migraine ($P < 0.001$).

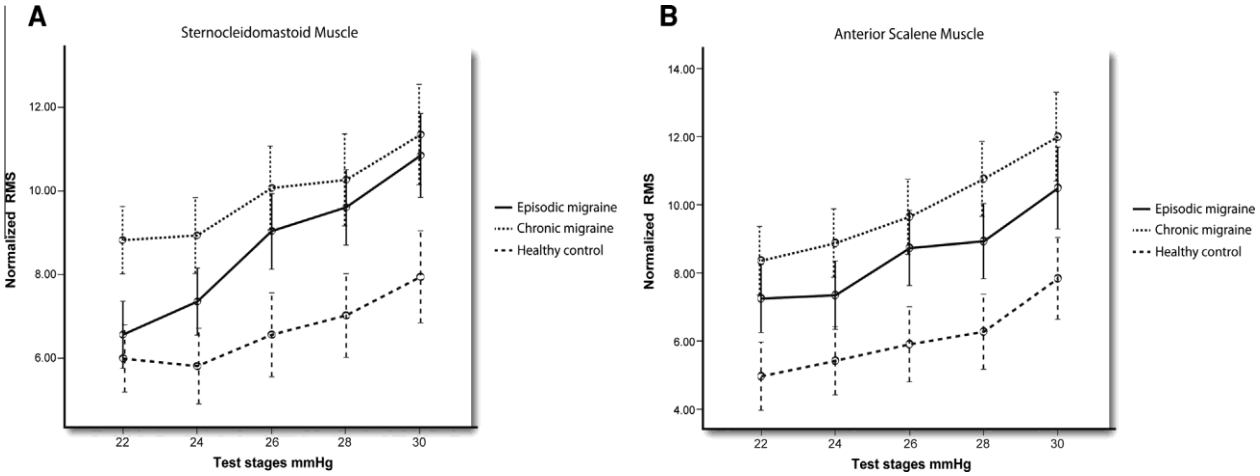

Fig. 2. The normalized root mean square (RMS) values for the sternocleidomastoid (A) and anterior scalene (B) muscles for the five stages of the cranio-cervical flexion test in the migraine and control groups. Values for the left and right muscles have been averaged. Data are expressed as means and standard error of measurement (SEM).

3.3. Neck extensor activity

The normalized RMS values for SPLEN and UT muscles during the stages of the CCFT in both patients and controls are presented in Fig. 3. There was also an increase in EMG amplitude of both SPLEN ($F = 34.629$; $df = 1$; $P < 0.001$) and UT ($F = 23.703$;$df = 1$; $P < 0.001$) with the progressive stages of the test in all groups, but with greater activity in both migraine groups (SPLEN: $F = 3.149$, $df = 2$; $P = 0.045$; UT: $F = 3.369$, $df = 2$ $P = 0.041$): individuals with chronic, but not episodic, migraine exhibited greater activity of the SPLEN and UT compared to healthy controls ($P < 0.01$). The presence of neck pain (SPLEN: $F = 0.833$, $df = 4$, $P = 0.440$; UT: $F = 1.145$, $df = 4$, $P = 0.326$) or neck-related disability (SPLEN: $F = 0.346$, $df = 4$, $P = 0.559$; UT: $F = 0.247$, $df = 4$, $P = 0.621$) did not exert any influence In all CCFT stages, differences for UT muscle were large between patients with chronic migraine and controls (d: 0.8–0.9); moderate between those with episodic migraine and controls (d: 0.5–0.6), but small between migraine sub-forms ($d < 0.5$). SPLEN activity demonstrated small effect sizes for most comparisons ($d < 0.5$).

4. Discussion

Women with chronic, but not episodic, migraine exhibited increased activity of their superficial neck extensor muscles during low-load cranio-cervical flexion contractions. No differences in the activity of the superficial neck flexors were observed between women with migraine (neither chronic nor episodic) and healthy controls.

The observation that superficial neck flexor muscle activity was not different in migraine patients compared to healthy subjects is consistent with earlier findings (Jull et al., 2007; Zito et al., 2006) suggesting that migraine sufferers do not exhibit the pattern of performance during CCFT expected for individuals with primary neck disorders (Falla, 2004; Jull et al., 2007; Zito et al., 2006). However, as known, migraine is not a primary neck disorder but rather is linked to brain dysfunction with deficient pain modulation that facilitates pain in the neck. It may, therefore, be surprising that increased activity of the antagonist could be evidenced only in chronic migraine despite of the high rates of neck pain in both migraine groups. This suggests that motor adaptation might be associated with migraine chronification as observed for more severe neck-related disability (Florencio et al., 2014).

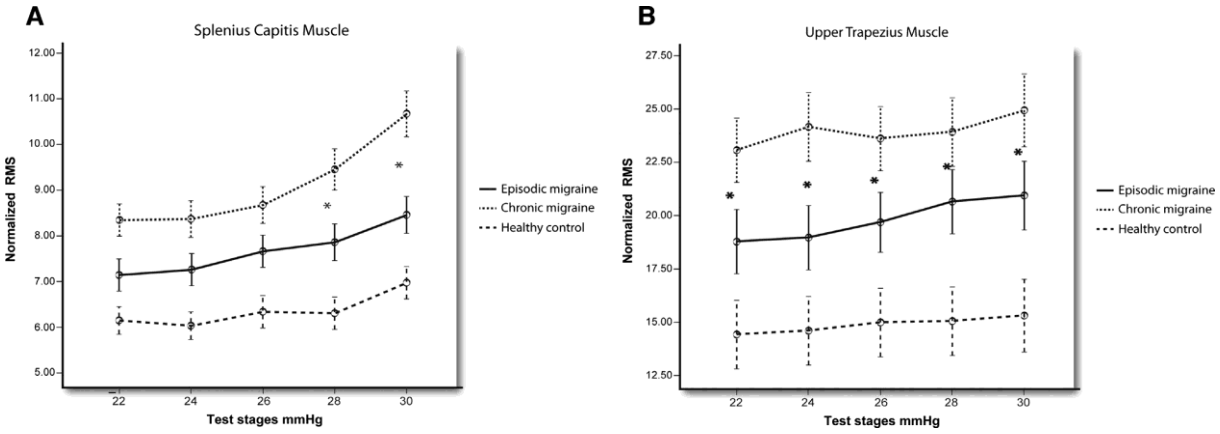

Fig. 3. The normalized root mean square (RMS) values for the splenius capitis (A) and upper trapezius (B) muscles for the five stages of the cranio-cervical flexion test in the migraine and control groups. Values for the left and right muscles have been averaged. Data are expressed as means and standard error of measurement (SEM)./P < 0.05.

It is possible that prolonged pain perceived in the neck region, regardless of the origin of the pain, induces changes in the behavior of cervical muscles or the way that the patient performs neck movement (e.g., fear of provoking pain or headache). Similar to our findings, increased muscle co-activation is one example of (mal) adaptive changes in neck muscle behaviour that has been seen in other primary headaches. In fact, Fernández-de-las-Peñas et al. (2008) observed that women with chronic tension-type head- ache displayed greater activation of the SPLEN muscle (antagonist) during isometric cervical flexion contractions compared to healthy women. Thus, increased activation of antagonist muscles seems to be a common motor adaptation in primary headaches exhibiting central sensitization.

The current study is the first one to investigate extensor muscle activation during the CCFT. The neck extensors activated progressively, similar to the superficial neck flexors during CCFT stages. Also, chronic migraine group demonstrated an increased activation of the SPLEN and UT muscles during CCFT reflecting a greater level of co-activation between flexor and extensor muscles. Women with chronic migraine demonstrated significantly higher activity of their neck extensors which was the equivalent of 3% MVC for SPLEN and 4–6% MVC for the UT. Although it is a discrete difference, when observing the activity expected for the control group, it represents 50% higher activity for SPLEN and 30% higher activity for the UT than that of the people without headache performing the CCFT. Since increased activity of superficial neck extensor muscles is not considered to be a sign associated with poor activation of the deep cervical flexors, the presence of inefficient control of the deep cervical flexors cannot be confirmed in migraine in the current study.

According to a recent theory of motor adaptation to pain, nociception can induce a redistribution of the activity within and between muscles (Hodges and Tucker, 2011; Hodges and Falla, 2015). Some experimental human pain studies have shown that pain induces reorganization of the motor strategy characterized by reduced activity of agonist muscles and increased activity of antagonist muscles (Graven-Nielsen et al., 1997; Lund et al., 1991) with the effect of reducing velocity and range of movement. Thus, the strategy may be one of protection for fear of pain (Hodges and Tucker, 2011). Indeed, studies have shown the same changes in motor strategies regardless of whether a person is experiencing or anticipating pain (Tucker et al., 2012).

Regardless of the mechanism underlying increased activation of SPLEN and UT muscles during sub-maximal cranio-cervical flexion contractions in individuals with chronic migraine, increased level of antagonist muscle co-activation has the potential to perpetuation neck pain (Hodges and Tucker, 2011). Increased activity implies muscle overload and changes in the load distribution on the neck and cranio-cervical region. Thus, increased neck muscle co-activation has the potential to contribute to the chronicity of neck signs and symptoms observed in migraine. Interestingly, the amount of antagonist co-activation was not related to the presence of neck pain or neck-related disability in our study but rather, whether the migraine was chronic or episodic reinforcing that this (mal) adaptive strategy might be dependent on the degree of chronicity.

Although this study expands current knowledge about changes in muscle activation in migraine, potential limitations should be recognized. First, we used maximal voluntary contractions to normalize EMG data rather than a submaximal contraction, such as a head lift. The major criticism about this reference is that patients with migraine might be less willing to perform a maximal contraction which would have underestimated their true maximum. However, one would expect that patients would have behaved the same during both maximum flexion and extension contractions thus both normalized flexor and extensor muscle EMG amplitude would be greater within patient groups than in controls, which was not the case. Second, characteristics of our sample limits generalization of the results as subjects were recruited from a tertiary centre and only women were included; so we do not know if the same results would be observed in community-based population or in men. Third, we conducted a task that may not represent muscular demands during daily life activities. But it was selected because it is commonly used to investigate the presence of neck muscle impairments in people with neck pain (Falla, 2004; Jull et al., 2004; O'Leary et al., 2007) and its validity and reliability has been well documented (Jørgensen et al., 2014). Fourth,

psychological features, such as fear of movement were not included and may have proven useful in understanding mechanisms underlying the observed increased muscle co-activation in the participants with chronic migraine. Finally, it is also possible that statistical power, according to observed Cohen's d effect sizes, was inappropriate for all comparisons between patients with chronic and episodic migraine. The same may have occurred with the comparisons between episodic migraine and healthy controls, except for UT muscle in all CCFT stages. Additionally, the large variation of EMG amplitude values within groups may have contributed to the lack of significant difference between them.

5. Conclusion

The current study found that women with chronic, but not those with episodic, migraine exhibited increased activity of their neck extensors acting as antagonists during the low load task of cranio-cervical flexion. No differences in the activation of the superficial neck flexors were observed

Conflicts of interest

We declare that there are no conflicts of interest.

Acknowledgments

The authors acknowledge The Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for the founding and the Head- ache and Craniofacial Disorders Ambulatory for the contribution, especially Professor José Geraldo Speciali.

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3.3 Article 3 – Published at Headache 2015;55:1312-1322

Cervical Muscle Strength and Muscle Coactivation During Isometric Contractions in Patients With Migraine: A Cross-Sectional Study

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Objectives.—This cross-sectional study investigated potential differences in cervical musculature in groups of migraine headaches vs. non-headache controls. Differences in cervical muscle strength and antagonist coactivation during maximal isometric voluntary contraction (MIVC) were analyzed between individuals with migraine and non-headache subjects and relationships between force with migraine and neck pain clinical aspects.

Method.—A customized hand-held dynamometer was used to assess cervical flexion, extension, and bilateral lateral flexion strength in subjects with episodic migraine (n=31), chronic migraine (n = 21) and healthy controls (n= 31). Surface electromyography (EMG) from sternocleidomastoid, anterior scalene, and splenius capitis muscles were recorded during MIVC to evaluate antagonist coactivation. Comparison of main outcomes among groups was conducted with one-way analysis of covariance with the presence of neck pain as covariable. Correlations between peak force and clinical variables were demonstrated by Spearman's coefficient.

Results.—Chronic migraine subjects exhibited lower cervical extension force (mean diff. from controls: 4.4 N/kg; mean diff from episodic migraine: 3.7 N/kg; P = .006) and spent significantly more time to generate peak force during cervical flexion (mean diff. from controls: 0.5 seconds; P = .025) and left lateral-flexion (mean diff. from controls: 0.4 seconds; mean diff. from episodic migraine: 0.5 seconds; P = .007). Both migraine groups showed significantly higher antagonist muscle coactivity of the splenius

capitis muscle (mean diff. from controls: 20%MIVC, P = .03) during cervical flexion relative to healthy controls. Cervical extension peak force was moderately associated with the migraine frequency (rs: -0.30, P = .034), neck pain frequency (rs:-0.26, P = .020), and neck pain intensity (rs:-0.27, P = .012).

Conclusion.—Patients with chronic migraine exhibit altered muscle performance, took longer to reach peak of force during some cervical movements, and had higher coactivation of the splenius capitis during maximal isometric cervical flex- ion contraction. Finally, patients with migraine reported the presence of neck and head pain complaints during maximal isometric voluntary cervical contractions.

Key words: migraine, cervical spine, surface electromyography, isometric contraction

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Accepted for publication July 10, 2015.

Conflict of Interest: The Authors declare that there is no conflict of interest.

Abbreviations: %MIVC antagonist percentages of antagonist activity during maximal isometric voluntary contraction, ANOVA one-way analysis of variance, EMG electromyography, HHD hand-held dynamometer, ICC intra-class correlation coefficient, ICHD-II second edition of International Headache Society criteria, MIVC maximal isometric voluntary contraction, RMS root mean square, SCM sternocleidomastoid muscle

(Headache 2015;55:1312-1322) doi: 10.1111/head.12644

INTRODUCTION

Cervical spine dysfunction is a collective term that includes many clinical disorders of the musculoskeletal structures of the cervical spine, with neck pain being the main symptom.[1] Although cervical spine dysfunction is usually considered to be common in tension type or cervicogenic headache,[2,3] individuals with migraine are substantially more likely to report neck pain than individuals without headache.[4,5] Furthermore, there is a positive correlation between neck pain and migraine frequency.[6,7] Convergence of afferent neurons from the upper cervical nerve roots (C1–C3) and the trigeminal nerve into the trigemino-cervical nucleus caudalis may explain the mutual influence of cervical and trigeminal pain.[8-10] Neck pain also influences the response to migraine acute therapy and overall disability.[11-14] While several studies focused on self-reported neck pain, objective measures of range of motion, upper cervical spine stiffness, hyperalgesia, and allodynia supported the concept that neck pain and migraine mutually influence each other.[15-20] However there is a paucity of investigations about the cervical musculature function in adults with migraine, even though the presence of neck pain has been associated with decreased muscle strength and higher antagonist muscle coactivation.[21-23]

Jull et al compared different types of headache with healthy controls and found that neck muscle weakness, restricted cervical range of extension, increased activity of neck muscles, and painful palpation of upper cervical joints were specific findings of individuals with cervicogenic headache.[24] However, evidence of weakness of cervical muscles for tension-type headache and restricted cervical range of motion in migraine and tension-type headache found in other studies[15,17,25-27] refutes the discriminating ability of these patterns.

Accordingly, the main objective of this study was to compare neck muscle strength and cervical musculature coactivation during maximal isometric voluntary contractions (MIVC) between individuals with migraine and non-headache subjects. A secondary aim was to correlate muscle force with clinical aspects of migraine and self-reported neck pain. The hypothesis was that individuals with migraine exhibit cervical muscle disorders, as assessed by strength outcomes and agonist/antagonist myoelectric activity as compared to healthy subjects. It will be also expected that chronic migraine patients will exhibit worse musculoskeletal findings than those with episodic migraine.

METHODS

Participants.—Patients with migraine aged between 18 and 55 years old were recruited from a tertiary university-based hospital between January and October 2014. They were invited to enroll in this study. Migraine patients were diagnosed following the second edition of International Headache Society criteria (ICHD-II) by an experienced neurologist. To avoid overlapping between groups, we included subjects with episodic migraine with less than 10 days of headache per month while chronic migraine had at least 15 days per month. Exclusion criteria included: 1, presence of other headaches; 2, medication overuse; 3, history of neck/head trauma (ie, whiplash); 4, history of cervical herniated disk or cervical vertebrae arthrosis according to medical records; 5, anesthetic block in the past month; or 6, pregnancy. In addition, a control healthy group without migraine history matched by age to the migraine group was also included. All participants in the current study signed the informed consent form before their inclusion. The local Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirao Preto (Brazil), approved the study design (process 16692/2012).

As no quantitative data were available in the literature to estimate differences or expected means of migraine group, sample size determinations were performed based on force mean and standard deviation of a pilot study (n = 7 at each group). Calculations were made adopting an alpha level of 0.05, and a power of 80%,[28] and a sample size of at least 20 participants in each group were needed to con- template differences. The observed effect sizes of the pilot study (Cohen's d) were 1.24 for flexion, 0.80 for extension, 0.81 for right, and 0.45 for left lateral-flexions considering healthy controls vs episodic migraine; 0.89 for flexion, 0.69 for extension, 1.03 for right, and 0.46 for left lateral-flexions for the comparison between healthy controls and patients with chronic migraine, and 0.33 for flexion, 0.36 for extension, 0.25 for right, and 0.68 for left lateral-flexion for episodic vs chronic migraine.

Procedures.—Participants were recruited and questioned by an examiner about demographic and clinical data including headache frequency (days/ month), self-report intensity of the pain (numerical pain rate scale, 0–10), years with migraine, and self- report neck pain, including report of frequency, intensity, and years with neck pain. The evaluation was held when all migraine patients were headache-free.

Wireless surface sensors (Trigno^{TM} Wireless System, Delsys Inc., Boston, MA, USA) were firmly fixed with adhesive tape bilaterally over: (1) the sternal head, 1/3 distal of the muscle belly of the sternocleidomastoid muscle (SCM)[29]; (2) the anterior scalene muscles, third portion of the muscle belly parallel to the clavicular head of the SCM[29]; and (3) the

splenius capitis muscles: palpable portion between upper trapezius and SCM located between 6 and 8 cm lateral of median line at level of C4.[30]

The skin was properly cleaned with alcohol and trichotomized. Myoelectric signals were acquired by EMGworks Acquisition (Delsys Inc.), amplified (gain 5 300) and sampled at 4000 Hz per channel. Then, aquisition of electromyography (EMG) activity of cervical muscles was synchronized with MIVC measurements.

MIVC measurements were held by a trained examiner blinded to the clinical diagnosis of the subjects, using a customized hand-held dynamometer (HHD) (model 01163; Lafayette Instrument Company, Lafayette, IN, USA) with a measurement range of 0–136.1 kg and an accuracy of 1% over full scale. The HHD was connected to a non- elastic belt to avoid external force records provided by examiner's hand during stabilization.[31,32]

One sub-maximal contraction was performed to familiarization with the task. Data were obtained from 3 repetitions of cervical flexion, extension and bilateral lateral flexion MIVC, lasting 3 seconds each repetition, with a 15 seconds rest period between repetitions and 2 minutes between con- tractions. The order of assessment was randomly chosen by drawing. The examiner provided standardized verbal encouragement during the contraction records. For each trial, peak force, time to produce the peak force, and neck and head-referred pain intensities were registered.

For cervical flexion contraction, subjects were positioned in supine, with full-extended knees, head and neck in a neutral position. To reduce compensations, one VELCRO® (VELCRO B.V., Manchester, NH, USA) belt was fastened tightly crossing the pelvis over the anterior superior iliac spine and other crossing the chest over the sternum. HHD was positioned in a frontal bone mean line. For cervical extension contraction, subjects were positioned in prone, with arms alongside the trunk. VELCRO® belts were fastened tightly, crossing the pelvis over the posterior superior iliac spine and other crossing the chest at T3 level. HHD was positioned at a mean line of the occipital protuberance. For cervical lateral-flexion contraction, individuals were positioned in lateral decubitus, with arms alongside the trunk. VELCRO® belts were positioned at greater trochanter and T3 levels. A height-adjustable pillow was placed to maintain neck and head at neutral position at sagittal plane. The HHD was positioned at the temporal bone, 2 cm above the helix ear (Fig. 1).

Maximal value of three repetitions for each movement was adopted as the maximal voluntary isometric force generated and used for comparisons purposes. As peak force was recorded in kgf, we converted it into N and normalized by the subject's body mass. The conversion formula used was: (HHD reading (kgf)* 9.81)/body mass (kg).

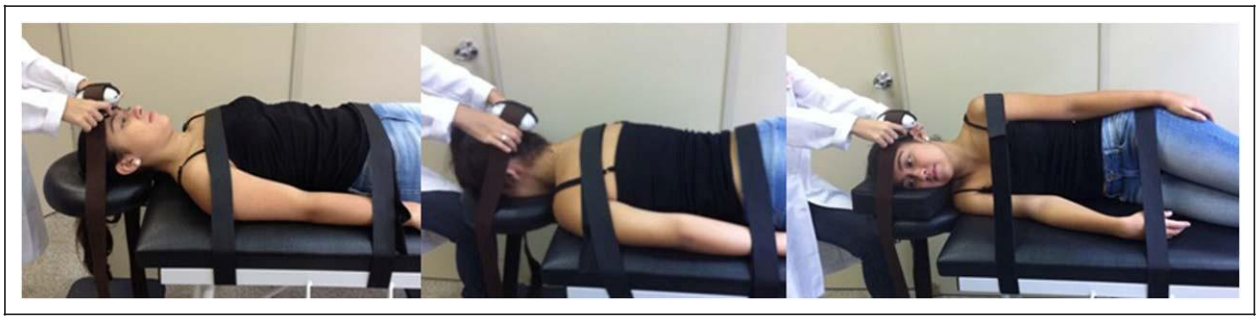

Fig. 1.—Position for strength measurements with an adapted hand-held dynamometer for maximal isometric contractions at cervical flexion, cervical extension, and cervical lateral flexion directions.

As cervical strength reliability is described as vulnerable to examiner bias,[33,34] prior to the data collection, intra-examiner reliability was first tested in 25 women (18 healthy women and 7 migraine) within a seven day interval. Retests were performed at the same day period using the same contractions order of the first evaluation.

Electromyography Data Processing.—Data were analyzed using EMGworks Analysis software (Delsys Inc.). EMGs raw signals were band-filtered a 20–500 Hz (fourth-order Butterworth) and the root mean square (RMS) were calculated from a 2 second window of each MIVC repetition. Antagonist muscle activity was normalized by its maximal RMS value obtained during the record of muscle activity when acting as agonist and described in percentages of antagonist activity during MIVC (%MIVC antagonist). For instance, SCM antagonist activity in neck extension was assessed by normalizing RMS during cervical extension by its RMS during cervical flexion. All EMG data were calculated from the same trial in which peak force was produced. The mean of both sides, right and left, were considered in the main analysis.

Statistical Analysis.—Data were analyzed with SAS® 9.2 software (SAS Institute, Cary, NC, USA) using PROC GLM. Means, standard deviation or 95% confidence intervals (95%CI) were calculated. Intraclass correlation coefficients ($ICC_{3,2}$) were calculated for verifying intra-examiner reliability of force measurements. Reliability was classified as poor (ICC $<$ 0.4), moderate (ICC ranging from 0.4 to 0.75), or excellent (ICC $>$ 0.75).[35]

A one-way analysis of variance (ANOVA) was used to determine the differences among groups for clinical outcomes, including age, neck pain, or years with disease. The comparison of the main outcomes among groups (peak force, %MIVC muscle coactivation) was conducted with a one-way analysis of covariance (ANCOVA) with the

presence of neck pain as covariable. For comparisons performed with ANCOVA among the three groups, the Bonferroni test was conducted as post hoc test analysis. Time to peak force and intensity of neck and head pain during cervical contractions were compared with Kruskal-Wallis test since these outcomes did not follow a normal distribution. Frequency of self- reported neck pain and frequency of symptoms complaints of neck and head pain during contractions were compared among groups using Fisher's association test. Finally, the Spearman's rho (r_S) test was used to determine correlation between clinical variables of neck pain and migraine with mean peak forces. Values <0.3 represent weak linear correlations; from 0.3 to 0.7 moderate correlations; and > 0.7 strong correlations.[36] The statistical analysis was conducted at 95% confidence level, and a P value < .05 was considered statistically significant.

RESULTS

Clinical Features of the Sample.— From 102 eligible subjects with migraine who accepted to participate, 50 were excluded. Reasons included concomitant headaches (n=19), receiving anesthetic block in the past month (n=16), reporting previous head/neck trauma (n=8), or unavailability to attend to the appointment (n=7). Finally, 52 patients with migraine, 31 with episodic migraine, and 21 with chronic migraine, participated.

Table 1.—Clinical and Demographic Characteristics of Patients With Episodic Migraine, Chronic Migraine, and Healthy Controls

	Healthy Controls (n=21)		Episodic Migraine (n=31)		Chronic Migraine (n=31)	
	Mean	95%CI	Mean	95%CI	Mean	95%CI
Age (years)	31	(27, 34)	33	(29, 37)	34	(30, 39)
BMI (kg/cm^2)	24.8	(23.1, 26.5)	25.2	(23.2, 27.2)	25.6	(23.9, 27.3)
Neck pain (n [%])†	6 (19%)		24(77%)		18 (86%)	
Time of onset (years)	5.6	(0.1, 11.2)	7.6	(5.1, 10.1)	5.4	(2.6, 8.2)
Frequency (days/month)	5.2	(0.7, 9.8)	10.7	(7.0,14.5)	18.5	(13.2, 23.8)
Intensity (0–10)†	3.8	(2.6, 5)	6.6	(5.7, 7.5)	6.2	(5.3, 7.0)
Migraine features						
Time of onset (years)			18.3	(14, 22.7)	16.1	(13.2, 19)
Frequency (days/month)††			5.9	(4.5, 7.2)	20.4	(18.0, 22.9)
Intensity (0–10)			7.6	(7.0, 8.2)	8	(7.2, 8.8)

†Significant differences between patients with migraine (both groups) and healthy controls (P<.001). ††Significant differences between patients with episodic and chronic migraine (t =-10.747; P < .001). BMI = body mass index.

Additionally, 31 healthy people were also included. The presence of self-reported neck pain was significantly higher (X^2= 30.391; P < .001) within the episodic (n = 24, 77%) or chronic (n = 18, 86%) migraine groups than within the control group (n = 6, 19%). The frequency (F = 10.612; P < .001) and intensity (F = 8.452; P < .001) of neck pain were also higher within both migraine groups as compared to healthy controls. Table 1 summarizes clinical and demographic data of each group.

Cervical Muscle Force.—The intra-rater reliability ($ICC_{3,2}$) of force measurements ranged from moderate to excellent: 0.78 for cervical flexion, 0.81 for cervical extension, 0.79 for right lateral-flexion, and 0.59 for left lateral-flexion.

Individuals with chronic migraine exhibited a significant reduction of force in cervical extension (F = 5.478; P = .006) than episodic migraine (mean diff: 3.7 N/Kg; 95%CI 1.4, 6.1) and healthy controls (mean difference: 4.4 N/kg; 95%CI 1.9, 6.8). No differences between episodic migraine and healthy control were observed (Bonferroni, P = .89, Table 2). No significant differences could be demonstrated for cervical flexion (F = 0.200; P = .82), right (F =2.108; P = .097) and left (F = 2.298; P = .11) cervical lateral-flexions among the groups (Table 2). Additionally, the presence of self-reported neck pain did not influence the analysis in any force out- come (P > .80).

Chronic migraine patients spent significantly more time to generate peak force during cervical flexion (F = 3.860; P = .045) than healthy control (mean difference: 0.5; 95%CI 0.1, 0.9 seconds; P = .025) and during left lateral-flexion (F = 4.480; P = .014) than subjects with episodic migraine (mean difference: 0.5; 95%CI 0.1, 0.8 seconds; P = .019) and healthy controls (mean difference: 0.4; 95%CI 0.1, 0.7 seconds; P = .042) (Table 2). No differences between episodic migraine and healthy controls were observed (Bonferroni, P > .77).

A higher number of individuals with chronic migraine reported complaints of neck and head pain during cervical contractions compared to episodic migraine and controls for all directions demonstrated in Figure 2; but, no significant differences in the intensity of the pain were reported (Table 2).

Table 2.—Means (95% Confidence Interval) of Maximal Peak Force (N and N/kg), Time Spent to Produce Peak Force and Pain During Execution of MIVC for Patients With Episodic and Chronic Migraine, and Healthy Controls

		Healthy Controls (n=31)	Episodic Migraine (n=31)	Chronic Migraine (n=21)	Neck Pain Influence
Cervical flexion	$Force_n$ (N/kg)	6.2 (5.6, 6.8)	6.3 (5.3, 7.2)	5.9 (5, 6.8)	F=50.389; P=.679
	Force (N)	41.5 (35.7, 47.4)	39.5 (34.3, 44.6)	40.1 (33.2, 46.9)	
	Time (seconds)	1.9 (1.6, 2.2)	2.0 (1.8, 2.3)	2.4 (2.1, 2.8)*	
	Pain to the head (0–10)	3.5 (2.5, 4.5)	5.5 (4.2, 6.8)	4.6 (2.6, 6.6)	
	Pain in the neck (0–10)	2.7 (1.1, 4.4)	5.5 (4.1, 6.9)	5.4 (4.4, 6.4)	
Cervical extension	Forcen (N/kg)	17.1 (15.8, 18.4)	16.4 (14.3, 18.6)	12.7 (10.9, 14.8)**	F=0.018; P=.982
	Force (N)	113.1 (102.4, 123.7)	104.1 (91.0, 117.2)	83.9 (72.2, 95.6)	
	Time (seconds)	2.6 (2.4, 2.8)	2.7 (2.6, 2.8)	2.9 (2.8, 3.0)	
	Pain to the head (0–10)	1.0 (NA)	5 (3.1, 6.9)	4.7 (2.5, 6.9)	
	Pain in the neck (0–10)	4.0 (2.0, 5.9)	7.1 (5.8, 8.5)	5.2 (4.1, 6.3)	
Cervical right lateral-flexion	Forcen (N/kg)	11.0 (9.7, 12.2)	10.6 (9, 12.2)	8.7 (7.4, 9.9)	F=0.05; P=.837
	Force (N)	72.5 (63.7, 81.2)	65.8 (57.6, 74.1)	58.3 (49.3, 67.3)	
	Time (seconds)	2.5 (2.3, 2.7)	2.4 (2.2, 2.6)	2.7 (2.5, 2.9)	
	Pain to the head (0–10)	4.0 (NA)	5.2 (4.0, 6.3)	7.4 (6.1, 8.8)	
	Pain in the neck (0–10)	5.0 (NA)	5.5 (4.0, 7.0)	4.7 (2.9, 6.5)	
Cervical left lateral-flexion	Forcen (N/kg)	10.3 (9.3, 11.4)	10 (8.4, 11.6)	8.2 (7.3, 9.2)	F=0.130; P=.878
	Force (N)	67.9 (60.8, 74.9)	61.7 (53.6, 69.8)	54.9 (48.3, 61.6)	
	Time (seconds)	2.4 (2.1, 2.6)	2.3 (2.1, 2.6)	2.8 (2.67, 2.92)**	
	Pain to the head (0–10)	5.0 (1.1, 8.9)	4.3 (3.7, 5.0)	4.3 (2.2, 6.5)	
	Pain in the neck (0–10)	2.7 (0.3, 5.0)	6.4 (4.7, 8.2)	5.3 (4.0, 6.5)	

*P<.05 compared to control group; **P<.05 compared to control and episodic migraine groups.
$Force_n$ = force normalized by the subject mass; NA = not applicable.

Antagonist Muscle Activation.—The ANOVA revealed significant higher %MIVC antagonist activity of the splenius capitis muscle during cervical flexion (F = 3.679; P = .03) in both migraine groups compared to healthy controls (mean difference chronic migraine: 21.4%; 95%CI 11.6, 31.2; mean difference episodic migraine: 18.9%; 95%CI 9.5, 38.3; P = .042) (Fig. 3). No significant differences among groups were found at %MIVC antagonist for the SCM during cervical extension (F = 0.884; P = .42), and for opposite scalene muscles during either left (F = 0.563; P = .57) or right (F = 1.735; P = .18) cervical lateral-flexion (Fig. 3).

Association Between Peak Force and Clinical Outcomes.—A significant moderate negative linear association between cervical extension peak force and the frequency of migraine attacks was observed (rs: -0.30; 95%CI -0.53, -0.02; P = .034): the higher the frequency of migraine attacks, the lower the peak force in cervical extension. Further, significant, but weak, linear associations between cervical extension peak force with neck pain frequency (rs: -0.26; 95%CI -0.45, -0.04, P = .020) and neck pain intensity (rs: -0.27; 95%CI -0.47, -0.06, P = .012) were also found: the higher the intensity or frequency of neck pain, the lower the peak force in cervical extension. No significant correlation existed between neck or migraine clinical features and peak force in cervical flexion, or both cervical lateral flexions (Table 3).

DISCUSSION

We found that individuals with chronic migraine exhibit reduced strength in the cervical extensor muscles and take a longer time to reach the peak of force on cervical flexion and left

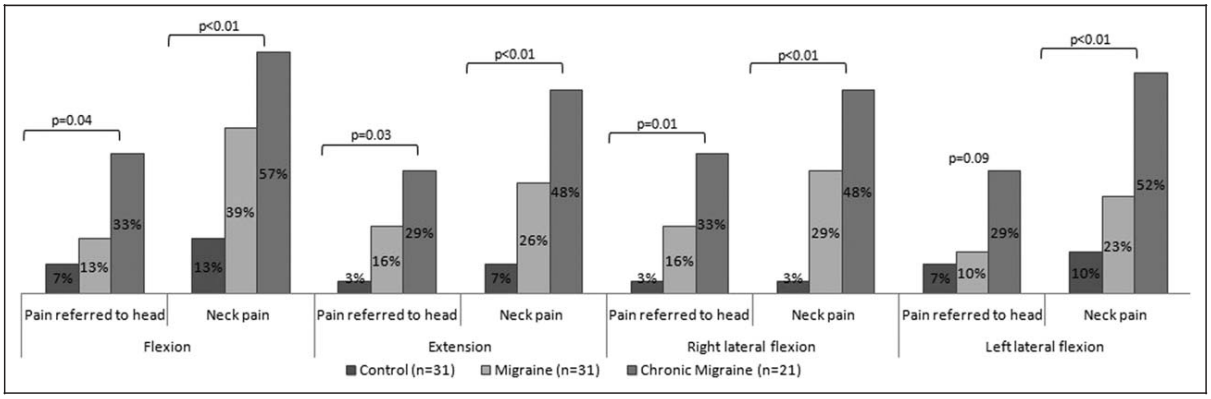

Fig. 2.—Frequency of pain complaints during maximal isometric contractions at all cervical directions. Proportions were compared with Fisher exact test.

lateral-flexion than subjects with episodic migraine or healthy controls. Maximal cervical muscle effort was associated with neck/head pain complaints more frequently in individuals with chronic migraine than those with episodic migraine or healthy people. Further, individuals with episodic/ chronic migraine exhibited higher coactivation of splenius capitis muscles during maximal cervical flexion contraction. These results would support the presence of altered muscle performance in the cervical musculature in chronic migraine, which reinforce that cervical spine dysfunctions may act as a perpetuating or contributing factor to headache chronification.

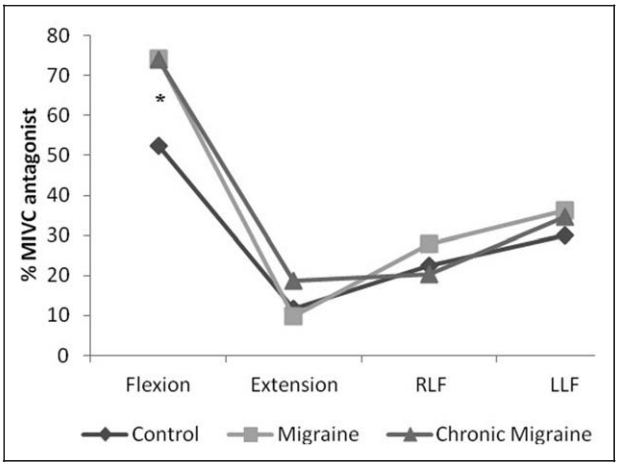

Fig. 3.—Antagonist activity of maximal isometric voluntary contractions (%MIVC antagonist) during peak force production in all cervical directions: flexion, extension, right lateral flexion, and left lateral flexion of patients with episodic migraine, chronic migraine and healthy controls. *Significant differences between patients with migraine (both groups) and healthy controls (ANOVA, $F = 3.679$; $P = .03$).

Our study suggests the presence of weakness of cervical extensor muscles, but adequate muscle force at cervical flexors in subjects with chronic migraine. Previous studies investigating cervical muscle strength in migraine did not observe differences between patients and healthy controls.[24,37] In fact, Jull et al found cervical muscle weakness only in adults with cervicogenic headache, but not in migraine or tension-type headache.[24] Our study demonstrated that individuals with chronic, but not with episodic, migraine exhibited lower cervical extensor muscle peak force. It is possible that discrepancies with previous studies are related to the fact that these studies did not distinguish between individuals with chronic or episodic migraine.[24,37] The relevance of the frequency of migraine was supported by the fact that the decrease in extension peak force was negatively associated with the number of migraine attacks suggesting a relationship between cervical muscle force production and chronification demonstrated in Figure 2; but, no significant differences in the intensity of the pain were reported (Table 2).of migraine.

An important finding was that cervical muscle peak force was not related to the presence of neck pain in our study supporting that differences among groups seem to be associated with the diagnosis of migraine. Nevertheless, weak associations between cervical extension peak force and the frequency

Table 3.—Correlations (Spearman Rho r_S [95% Confidence Interval]) Between Clinical Variables and Peak Force in All Cervical Spine Movements in Patients With Migraine (Data From Episodic and Chronic Migraine Were Pooled)

	Cervical Flexion	Cervical Extension	Cervical Right Lateral Flexion	Cervical Left Lateral Flexion
Neck Pain (n=48)				
Frequency	- 0.19 (-0.39, 0.03)	-0.26 (-0.45,- 0.04)*	-0.16 (-0.37, 0.05)	-0.16 (-0.37, 0.06)
Intensity	-0.12 (-0.33, 0.10)	-0.27 (-0.47, -0.06)**	-0.21 (-0.41, 0.01)	-0.23 (-0.43, -0.02)
Time of onset	-0.11 (-0.32, 0.11)	-0.09 (-0.30, -0.13)	-0.14 (-0.35, 0.07)	-0.22 (-0.42, -0.004)
Migraine (n=52)				
Frequency	0.02 (-0.25, 0.29)	-0.30 (-0.53,- 0.02)***	0.19 (0.44, 0.09)	-0.21 (-0.46, 0.06)
Intensity	0.19 (-0.09, 0.44)	0.03 (-0.25, 0.30)	0.06 (0.22, 0.32)	0.06 (-0.22, 0.33)
Time of onset	-0.06 (-0.33, 0.22)	0.11 (-0.17, 0.37)	0.04 (0.31, 0.24)	-0.09 (-0.35, 0.19)

*P=.020; **P=.012; ***P=.034.

and intensity of neck pain were also observed. These findings suggest that individuals with chronic migraine may show a similar pattern of decreased cervical extension peak force than those with idiopathic chronic neck pain,[21] although the impact of pain features on muscle strength is still controversial.[33]

Women with chronic migraine also showed longer time to produce similar peak force at cervical flexion and left lateral-flexion, suggesting the presence of altered muscle performance in this population. Although these differences were small (0.4 seconds), but considering nerve conduction velocity,[38] they could suggest different strategy of muscles fiber recruitment in patients with chronic migraine; so further investigations regarding neck muscle recruitment in migraine are clearly needed.

Almost half of the chronic migraine group reported neck pain and about a third of them reported head pain during cervical muscle contractions. As migraine is a dysfunction in nociceptive pain pathways with central sensitization promoting cephalic and extracephalic allodynia,[8,39] the source of pain reported during neck contractions can be

attributed to afferences from different structures located in the cervical region. But, considering that we asked for isometric contractions with individuals at anatomic positions, we can assume that articular components were not overloaded. In fact, the presence of referred pain to the head mimicking migraine attacks from stimulation of neck/shoulder muscles has been already observed.[15,40] Therefore, our hypothesis is that the tissue responsible for neck/head pain during maximal efforts would be the cervical musculature.

An important finding was that individuals with migraine exhibited higher coactivation of the splenius capitis muscle during cervical flexion. Current findings are similar to those previously found in patients with chronic tension-type headache,[25] but contrary to those observed in adolescent with migraine.[37] Increased antagonist muscle coactivation reflects a reorganization of the motor control strategy, which may be a consequence of the nociceptive barrage, and hence of the central sensitization observed in migraine. The presence of muscle coactivation of the splenius capitis muscle during cervical flexion may explain the decreased peak force in cervical extension, since the splenius capitis is the main extensor of the head and it is possible that this muscle can be overloaded and, therefore, fatigued in this population. The presence of increased muscle coactivation, a decreased isometric force, and the necessity of longer time to produce similar peak force in different directions would support general altered muscle performance of the cervical musculature in patients with migraine.

It is important to point out that muscle coactivation is not always a negative response for the cervical spine. This adaptive change of the neuromuscular system due to pain may be beneficial in the presence of an acute pain condition for protection purposes or to maintain proper motor output.[23,41] However, at long-term, muscle coactivation may reduce the function of the cervical spine, leading to greater compression of the joints, altering load distribution and consequently affecting the biomechanics of the head and the neck.[27,41,42]

Current findings have potential clinical contributions that help to guide physical therapy interventions in the management of migraine. For instance, our study suggests the necessity of proper identification of reduction of neck muscles force with special attention to cervical extensors in individuals with chronic migraine. In addition, manual examination of painful neck muscles is also recommended. The identification of these

musculoskeletal impairments can help to develop effective exercise programs for the management of patients with migraine.

This study has limitations and should be seen as a pilot. First, we cannot exclude that we under- powered some differences among groups due to the sample size. Second, the sample size forced us to conduct one-way tests and not to adjust for multiplicity. Since several comparisons were conducted, there is an important chance that some of the findings were spurious. Nevertheless, due to the overall coherence of the findings, the validity of the results remains. Subsequent work should increase the sample, adjust for multiplicity, and conduct two-way tests since we have now robust evidence to justify time and cost commitments. Third, maximal force and muscle coactivation during MIVC do not represent real cervical muscles demand during daily activities. Therefore, investigation of muscle endurance, feed-forward activation, and muscle coactivation during daily life activities should be investigated in this population.

CONCLUSIONS

This study revealed that patients with migraine, particularly those with the chronic form, exhibit altered muscle performance manifested as decreased cervical extensors peak force, the necessity of longer time to reach the peak of force, and the presence of higher coactivation of the cervical extensors during maximal isometric cervical flexion contractions. In addition, patients with migraine reported the presence of neck/head pain complaints during maximal isometric voluntary cervical contractions.

Acknowledgments: The authors acknowledge the Sao Paulo Research Foundation (FAPESP) for the financial support and members of Headache and Craniofacial Disorders Ambulatory for the contribution, especially Professor Jos e Geraldo Speciali. First author received a grant to develop this research from The Sao Paulo Research Foundation (FAPESP).

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3.4 Article 4- Submitted at Clinical Biomechanics

Title Page

Title

Time and frequency-domain analysis of neck muscles electrical activity during maximal isometric contractions in migraine patients: a controlled study.

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Time and frequency-domain analysis of neck muscles electrical activity during maximal isometric contractions in migraine patients: a controlled study.

Abstract

Background: Neck pain and musculoskeletal impairments are usually seen in patients with migraine. However, no previous study verified the relationship between neck muscles activity and the frequency of migraine attacks.

Objective: To compare time and frequency-domain of the electrical activity of neck muscles during maximal isometric voluntary contractions (MIVC) in subjects with episodic migraine, chronic migraine and controls.

Design: cross-sectional study.

Methods: Thirty-one women with episodic migraine, 21 with chronic migraine and 31 non-headache controls performed MIVC in cervical flexion and extension. The surface electromyography from splenius capitis, upper trapezius, sternocleidomastoid and anterior scalene were acquired simultaneously. Force production was assessed with a customized hand-held dynamometer. Median frequency (MDF), change of median frequency over sustained time (slope) and normalized root mean square were calculated. Comparison among groups was performed by ANOVA with Bonferroni´s *post-hoc* test, adopting a significance level of 0.05.

Results: Both migraine groups demonstrated a decrease of upper trapezius MDF during extension while the control group presented an increase (F=7.179; P=0.001). Episodic migraine had greater average MDF of upper trapezius at extension (F= 8.118; P=0.001) and lower activity in sternocleidomastoid at cervical flexion when compared to controls (F=

4.457; P=0.015). Also, chronic migraine produced lower extension force output compared to both episodic migraine and control groups (F=4.870; P=0.010).

Limitations: MIVC might not reflect the typical muscle demand and the profile of the patients from a tertiary headache center may be more severe than expected from general population.

Conclusion: Women with migraine present altered neck muscle activation than controls and greater fatigability, particularly in cervical extensors, during a sustained isometric contraction. Chronicity of migraine attacks was associated with lower force production compared to controls.

Key-words: fatigue, cervical spine, headache.

Abstract word count: 275

Manuscript word count: 2.529

Time and frequency-domain analysis of neck muscles electrical activity during maximal isometric contractions in migraine patients: a controlled study.

INTRODUCTION

Migraine is a primary headache disorder associated with recurrent episodes of pain.[1,2] It is classified as chronic migraine when headache episodes fulfilling migraine features occur more than 15 days per month and episodic migraine when the frequency of pain attacks is less than 15 days per month.[3] Migraine-like headache is typically unilateral, throbbing quality, moderate-severe on intensity, aggravated by routine physical activity, and can last between 4 to 72 hours. According to the diagnostic criteria, headache must be also associated with autonomic (nausea or vomiting) and sensory (photophobia and phonophobia) symptoms.[3] However, it can be accompanied by other types of autonomic or sensory symptoms and usually affective (depressive and irritability) or cognitive (i.e. attention deficit) aspects are also involved.[4]

Among all sensory associated symptoms, particular attention has been drawn to the presence neck pain and/or neck stiffness as comorbid conditions or premonitory symptoms.[5-12] Population-based studies has demonstrated that migraine subjects are 2 to 5-fold likely to suffer from neck pain than headache-free subjects.[10,12] Also, prevalence of self-reported neck pain as an associated symptom is higher even than the frequency of nausea, a sensory symptom included in the diagnostic criteria.[13] Nevertheless, there is no consensus determining if neck pain is a premonitory symptom and/or part of the own migraine attack.[9]

Migraine physiopathology is characterized by generalized neuronal hyper-excitability as a result of the combination of inhibitory/excitatory imbalance and central/peripheral sensitization processes with a primary role of the trigemino-vascular pain pathways and brainstem.[14] The interaction between migraine and neck pain is neurophysiologically supported by sensitization of the second order neurons located in the trigemino-cervical nucleus caudalis that receive afferences from meninges, trigeminal, and upper cervical nerve roots.[15]

Similar to other chronic pain conditions, it would be expected that the experience of neck pain would be associated with an altered neck muscles performance and altered motor control strategies.[16,17] There are few studies investigating motor control disorders of the neck muscles in migraine sufferers. Subjects with migraine have demonstrated higher antagonist muscle

coactivation and lower force production of cervical extensors during a low-level cranio-cervical flexion task as compared to healthy people. [18-20] Most of these findings were only observed in subjects with chronic migraine. Other previous studies that included only episodic migraine or did not differentiate between migraine subtype (episodic or chronic) reported no differences on neck muscles activity and force production between patients and controls.[21-24]
Although episodic and chronic migraine diagnosis is delimited by the frequency of migraine episodes, there are socio-demographic differences and co-morbidity profiles as well as differences on brain structures aberrant changes.[25-27] These differences raise the discussion about whether episodic/chronic migraine are the same entity or different diseases process. [28] Therefore, it might be worthwhile to investigate differences between both subtypes separately.
Regarding electromyography (EMG) analysis domains, time domain analysis such as sEMG amplitude is the most common method studied. However, frequency domain analysis would be an objective assessment of fatigue especially considering time dependent changes in the median frequency (MDF) during sustained isometric tasks.[29,30] Amplitude and frequency along with force output would help to increase current knowledge about neuromuscular control motor in migraine. Thus, the aim of the current study was to investigate time and frequency-domain EMG analysis of the neck muscles and force output during maximal isometric voluntary contractions (MIVC) in headache-free controls and individuals with episodic or chronic migraine. These data would help to discuss mechanisms of neuromuscular control and muscle response such as electromyographic fatigue, amplitude of the electrical signal, and force production in this condition which may contribute to provide suitable and more specific rehabilitation goals with focused attention to the migraine frequency chronification.

METHODS

Study design and participants

This study consisted of a pre-planned secondary analysis of a cross-sectional study that aimed to investigate neck muscle features of women with migraine. It is specifically focused on neck muscles activity during MIVCs and included the EMG analysis of the frequency and amplitude of the signal along with information regarding the force output resulting from the muscle contraction.

Sample size was determined a priori based on force data of a pilot study (n=7 in each group) adopting an alpha level of 0.05, and a power of 80%. Sample calculation required at least 20 participants on each group.

Participant's recruitment was performed in a university-based hospital between January to October 2014. Migraine diagnosis was made by neurologists with expertise in headache management according to the third edition beta version of the International Headache Society criteria.[3] The episodic migraine group was composed by women with less than 10 episodes per month and those with 15 or more days of migraine per month were included at the chronic migraine group. Subjects were excluded if they underwent an anesthetic nerve block the previous year or if they present any concomitant headache, degenerative cervical conditions, history of trauma at neck and/or face, or pregnancy. The same inclusion and exclusion criteria were applied to enroll subjects to the control group without migraine history, among local community. All subjects who accepted to participate signed the informed consent. The study design was approved by local Ethics Committee (process 16692/2012).

Demographic and clinical data were collected during a personal interview and included migraine episodes (days/month), intensity of migraine attacks (numerical pain rate scale [NPRS], 0-10), history (years) of disease, and self-report neck pain, including report of frequency, intensity and years with neck pain

Procedures

Subjects were assessed in a pain-free period by a trained and examiner blinded to the subject's condition. A customized hand-held dynamometer (HHD) (model 01163; Lafayette Instrument Company, Lafayette, Ind., USA) was used for MIVC assessments. The HHD was connected to a non-elastic belt for avoiding the addition of the force provided by the examiner hand during stabilization. Subjects were positioned in supine with a non-elastic belt tightly fastened crossing the pelvis over the anterior superior iliac spine and another one crossing the chest over the sternum for flexion assessment. For extension assessment, subjects were in prone with the belt crossing the pelvis over the posterior superior iliac spine and another one over the chest at T3 level.

Subjects were familiarized with the test positions by performing a submaximal contraction. Then, three repetitions of MIVC sustained for 3 seconds of cervical flexion and extension were conducted. Trials were performed with a 15sec rest period between repetitions and 2min between test conditions. The order of movements was randomly allocated by drawling. The examiner provided a standardized verbal encouragement during the contraction records. As the HHD provided the peak force value in kgf, data were multiplied by 9.81 to convert into N,

and normalized by the subject's body mass (Kg). Mean values of the 3 repetitions for each movement was used for between-groups comparisons.

Electromyography (EMG) data acquisition and processing

Surface EMG was acquired using the TrignoTM Wireless System (CMRR of 80 dB, input impedance exceeding 1000Ω, Delsys Inc. Boston, MA, USA). Each Trigno sensor is composed by two parallels groups with two bars each one (Ag-AgCl), with a fixed inter-electrode distance of 10 mm. Sensors were firmly fixed with adhesive tape bilaterally after proper skin cleaning (cleaned with alcohol and tricotomized when necessary). Neck muscles included were sternocleidomastoid, anterior scalene, splenius capitis and upper trapezius. Electrodes were placed according to standard instructions described by Falla et al[31] and Somerich et al;[32] since only upper trapezius muscle is present in the SENIAM recommendations.[33] Myoelectric signals were acquired, digitalized, amplified (gain=300), band-pass filtered (20-450Hz with 40 and 80 dB/dec) and sampled at 4kHz per channel with a 16bit resolution A/D by software *EMGworks Acquisition* (Delsys Inc. Boston, MA, USA).

Data were analyzed using a customized MATLAB code (The Mathworks™, Natick, MA, USA). EMGs raw signals were band-filtered at 20-500Hz (4th order Butterworth). Time domain analysis was performed in a 2sec window and amplitude represented by the average root-mean-square (RMS) was calculated. Highest EMG value of each MIVC (peak) was used to normalize EMG data from each trial. MDF is a spectral index derived from raw signal by the fast Fourier transform algorithm and represents the frequency that divide the power spectrum into two equal areas.[34] It was calculated using a moving window of 0.375s with an overlapping rate of 50%. Fatigue index (i.e. MDF slope) was determined using a linear best-fit analysis by identification of the angular coefficient. Negative values indicate that MDF is decreasing in function of time shifting the power spectrum density curve to lower rates of frequency. This shifting is representative of electromyographic fatigue.[30,35]

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Means and standard deviation were calculated for the descriptive analysis. Clinical outcomes were compared among groups using the one-way analysis of variance (ANOVA) with Bonferroni´s test as post hoc test analysis. The mean of both right and left sides and of the 3 repetitions for each muscle were considered in the main analysis. Hypothesis testing for the EMG variables (MDF, slope and normalized RMS) and normalized force were performed by one-way analysis of variance (ANOVA) comparing three groups. Bonferroni´s test was

conducted as post hoc test analysis. A level of significance of 0.05 was adopted for all statistical analysis.

RESULTS

From 102 eligible subjects with migraine who accepted to participate, 50 were excluded mostly frequent due to concomitant headaches diagnosis (n=19;38.0%) and anesthetic nerve block in the past month (n=16;32.0%). A total of 31 women with episodic migraine, 21 women with chronic migraine and 21 headache-free healthy women were included. A flow chart of the study has been previously reported.[19] Sample features are described in the **table 1**.

The ANOVA revealed significant differences in the MDF of the upper trapezius muscle during MIVC in cervical extension (F=8.118; P=0.001), but no in neck flexion (F=1.389; P=0.26). The post hoc analysis revealed higher MDF of the upper trapezius muscle in cervical extension in women with episodic migraine compared to headache-free women (P<0.001). The ANOVA did not observe significant differences for either flexion or extension in MDF of the sternocleidomastoid (flexion: F=0.254, P=0.77; extension: F=1.113, P=0.33), splenius capitis (flexion: F=0.616, P=0.54; extension: F=2.630, P=0.08), and anterior scalene (flexion: F=0.017, P=0.98; extension: F=1.102, P=0.34) muscles among the groups (**table 2**).

The slope analysis revealed that both migraine groups exhibited different pattern of muscle activity in the upper trapezius MDF than controls during extension (F=7.111; P=0.001). A decrease was found for both episodic (mean= -0.93; P=0.007) and chronic (mean= -1.22, P=0.005) migraine, while an increase was observed for the control group in the same interval-period (mean= 0.88) (**table 3**). No significant differences within the slope analysis was reported for the upper trapezius muscle in cervical flexion (F= 0.047, P=0.95). Finally, no significant differences for sternocleidomastoid (flexion: F=0.478; P=0.62; extension: F=0.047, P=0.95), anterior scalene (flexion: F=1.371, P=0.26; extension: F=0.984, P=0.38) and splenius capitis (flexion: F=0.659, P=0.52; extension: F=0.366, P=0.70) muscles were observed for either cervical flexion or extension.

Difference in the normalized RMS was observed for episodic migraine group as compared to healthy controls showing lower activity of the sternocleidomastoid muscle when acting as agonist during cervical flexion (F= 4.457; P=0.02), but not acting as an antagonist in cervical extension (F=1.889; P=0.15). No differences among groups in the amplitude of the signal were reported for the anterior scalene (flexion: F=0.401, P=0.67; extension: F=0.119,

P=0.89), the splenius capitis (flexion: F=1.333, P=0.27; extension: F=1.936, P=0.15) and upper trapezius (flexion: F=1.713, P=0.19; extension: F=1.768; P=0.18) muscles (**Figure 1**). Finally, extension force output was lower for chronic migraine compared to both episodic migraine and healthy controls (F=4.870; P=0.01). No differences in flexion strength were found among the groups (F=0.211; P=0.81) (**Figure 2**).

DISCUSSION

The current study found that women with migraine present a distinct pattern of muscle control activation compared to headache-free women exhibiting impairment of neuromuscular efficiency. Cervical extensors seem to be the most impaired muscular group as both migraine groups showed signs of fatigue in the upper trapezius muscle during a MIVC in cervical extension in contrast to headache-free controls. Additionally, women with episodic migraine exhibited greater MDF of the upper trapezius muscle, whereas women with chronic migraine exhibited lower extension force, but with similar median frequency and similar amplitude under the same conditions. Our findings may help to determine more specific interventions when addressing cervical dysfunctions in migraine treatments.

Only two studies have previously investigated frequency domain variables of the sternocleidomastoid muscle activity during long lasting (~20seconds) sustained head lift in episodic migraineurs. Both reported no differences between migraineurs and healthy controls regarding MDF and its slope.[23,24] Our results agree with these findings, since we observed that even at high load tasks sustained for a short period, neck superficial flexors of migraineurs does not seem to be exhibit susceptibility to electromyographic fatigue.

However, assessment of neck extensors of individuals with headache should be encouraged. Our findings indicate that the presence of the migraine was associated with cervical extensors susceptibility to early electromyographic fatigue. Also, chronicity of migraine would promote more severe motor adaptations such as lower force production of the cervical extensors. Reduced force production and early electromyographic fatigue of cervical extensor muscles is a common finding during the assessment of several other chronic conditions such as chronic neck pain and temporomandibular pain disroder.[36-42] Therefore, it may be suggested that neck pain associated with other pain conditions, generally associated with central sensitization, might present, as a common strategy, a functional and motor adaptation at superficial neck extensors.

Using a MIVC sustained for a short time period for assessing the muscle fatigue instead of using the widely used classical endurance tests for neck muscles may be seen as a limitation of the current study. However, endurance tests generally identify fatigues with a failure point, i.e., the point over time in which a muscle contraction can no longer be sustained. Consequence of identifying the failure point is that fatigue will be detected only after it have occurred.[30] Moreover, an endurance task maybe also be interrupted by behavioural factors such as fear of pain.[43] Changes in the power spectrum density are able to detect indications that precede failure and are recommended to assess muscles fatigability.[30]

Finally, although the current study increases current evidence related to motor control disturbances of the superficial neck extensor muscles in women with migraine, some potential limitations should be considered. First, our sample was composed by women with migraine recruited from a tertiary headache center which may overestimate the cervical-related dysfunctions described in our study. Second, the maximal isometric voluntary contraction might not reflect the typical muscle demand on daily life activities and investigations of neck muscles fatigue of patients with migraine during submaximal tasks might be of importance in future studies. Finally, our tests were performed in supine/prone position, hence, the effect of the head position in orthostatic posture that might predispose extensors overload in different head postures was not considered.

CONCLUSION

Women with migraine exhibited altered cervical muscle control and activation, especially at superficial neck extensors showing greater electrical fatigability, despite of chronicity of migraine. Lower force production with similar amplitude of myoelectrical signals was also present in women with migraine, but only in the chronic group. Current findings may help clinicians to better identification of neuromuscular deficiencies in the cervical muscles in patients with migraine for determining specific therapeutic programs.

ACKNOWLEDGMENTS

The authors acknowledge the members of the Headache and Craniofacial Disorders Ambulatory, especially Professor José Geraldo Speciali, for the availability to help us in the recruitment of the patients. Also, we would like to acknowledge the São Paulo Research Foundation for the grant provided to the first author to develop the project related to this manuscript (process number 2012/22245-2).

Conflict of interest: none declared.

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Table 1: Socio-demographic data and clinical presentation of women with migraine and headache-free controls

	Control (n=31)		**Episodic Migraine (n=31)**		**Chronic Migraine (n=21)**	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	31	9.1	33	11.2	34	9.7
BMI (kg/cm^2)	24.8	4.7	25.2	5.6	25.6	4.8
Neck pain [n (%)]*	6 (19%)		24 (77%)		18 (86%)	
Frequency (days/month)*	5.2	5.7	10.7	9.9	18.5	11.2
Intensity (0-10)*	3.8	1.5	6.6	2.2	6.2	1.8
Time of onset (years)	5.6	6.9	7.6	6.3	5.4	5.9
Migraine features						
Frequency (days/month) †			5.9	3.7	20.4	7.8
Intensity (0-10)			7.6	1.80	8	2.7
Time of onset (years)			18.3	12.2	16.1	8.7

BMI: Body mass index

* P<0.01 differences between both groups of women with migraine and controls.
† P<0.01 differences between women with episodic and chronic migraine.

Table 2: Median frequency of neck muscles during a sustained maximal voluntary contraction of episodic migraine (n=31), chronic migraine (n=21) and headache-free (n=31) women.

Median Frequency							
		Control (n=31)		Episodic Migraine (n=31)		Chronic Migraine (n=21)	
		Mean	SD	Mean	SD	Mean	SD
Flexion	SCM	106.10	11.85	106.86	13.46	104.38	10.66
	AS	115.32	19.74	115.36	14.48	116.14	16.79
	SPLEN	92.28	12.91	99.76	16.71	91.48	13.77
	UT	88.53	9.79	92.35	9.11	89.29	9.20
Extension	SPLEN	87.15	9.82	88.16	11.40	79.46	21.77
	UT	66.00	4.94	73.97*	10.10	70.14	7.25
	SCM	101.68	15.09	106.59	14.01	99.52	25.19
	AS	88.90	15.92	96.45	16.11	91.52	21.28

* $P<0.05$ compared to control group.

SCM= sternocleidomastoid; AS= anterior scalene; SPLEN= splenius capitis; UT= upper trapezius.

Table 3: Median frequency changes over the time represented by the slope (angular coefficient) of a linear regression model.

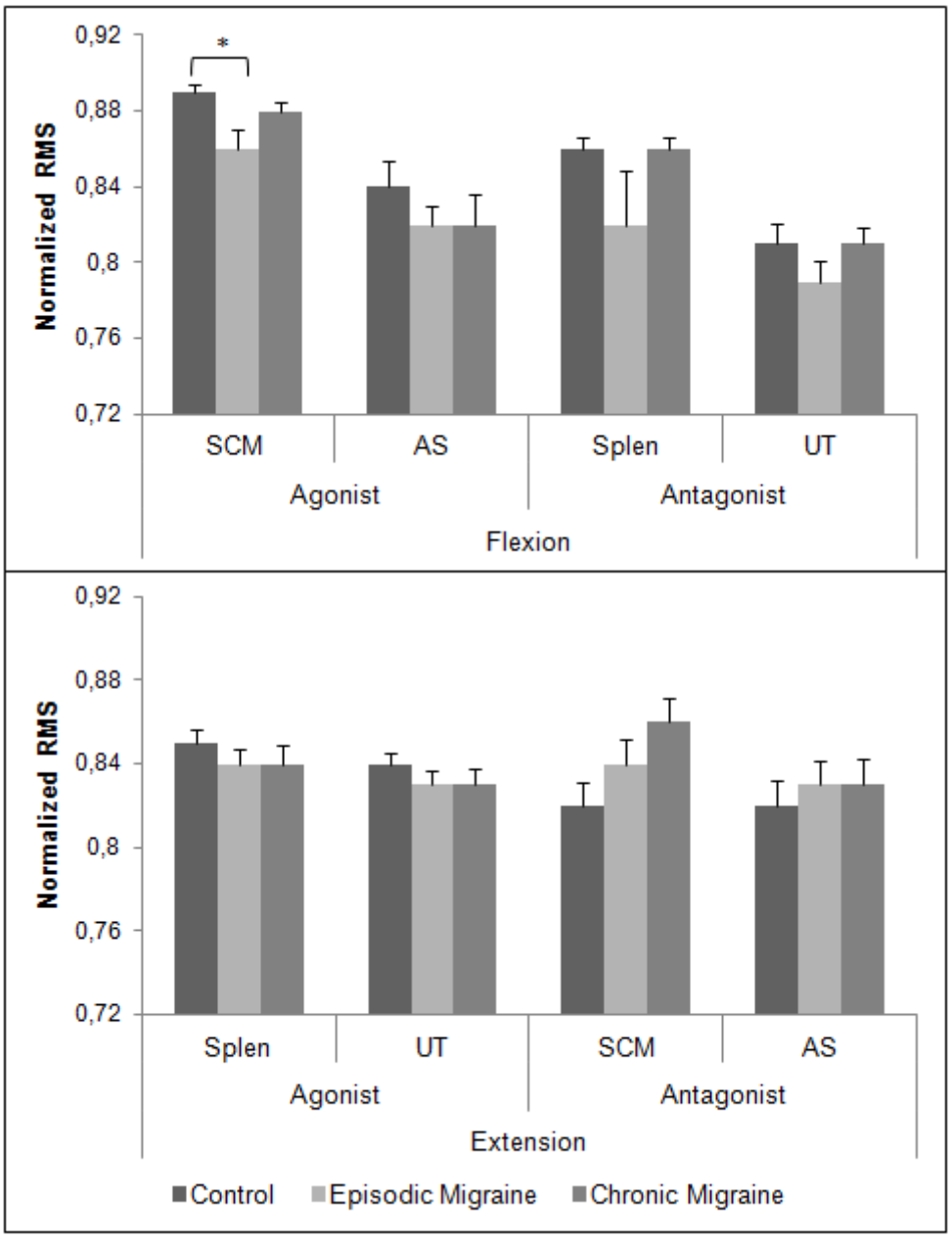
		SLOPE					
		Control (n=31)		Episodic Migraine (n=31)		Chronic Migraine (n=31)	
		Mean	SD	Mean	SD	Mean	SD
Flexion	SCM	-0.66	2.97	0.15	4.15	-0.08	2.45
	AS	0.26	3.97	-0.18	3.86	1.70	4.68
	SPLEN	0.58	2.91	1.42	3.22	1.00	2.16
	UT	1.43	2.79	1.30	3.83	1.12	4.07
Extension	SPLEN	0.69	3.60	0.08	2.75	0.29	1.39
	UT	0.88	2.44	-0.93*	2.07	-1.22*	2.34
	SCM	0.38	6.55	0.48	4.11	0.04	4.18
	AS	0.38	5.28	0.43	4.65	-1.25	3.69

* P<0.05 compared to control group.
SCM= sternocleidomastoid; AS= anterior scalene; SPLEN= splenius capitis; UT= upper trapezius.

FIGURE LEGENDS

Figure 1: Amplitude of electrical activity (normalized RMS) during maximal isometric voluntary contractions in cervical flexion and extension of women with episodic migraine (n=31), chronic migraine (n=21) and headache-free controls (n=31).
* P<0.05. SCM=sternocleidomastoid; AS=anterior scalene; SPLEN=splenius capitis; UT=upper trapezius.

Figure 2: Mean neck muscle force production (normalized by the body mass) during maximal isometric voluntary contractions in flexion and extension of women with episodic migraine (n=31), chronic migraine (n=21) and headache-free controls (n=31).
* P<0.05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0,92
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Splen
UT
SCM
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Agonist
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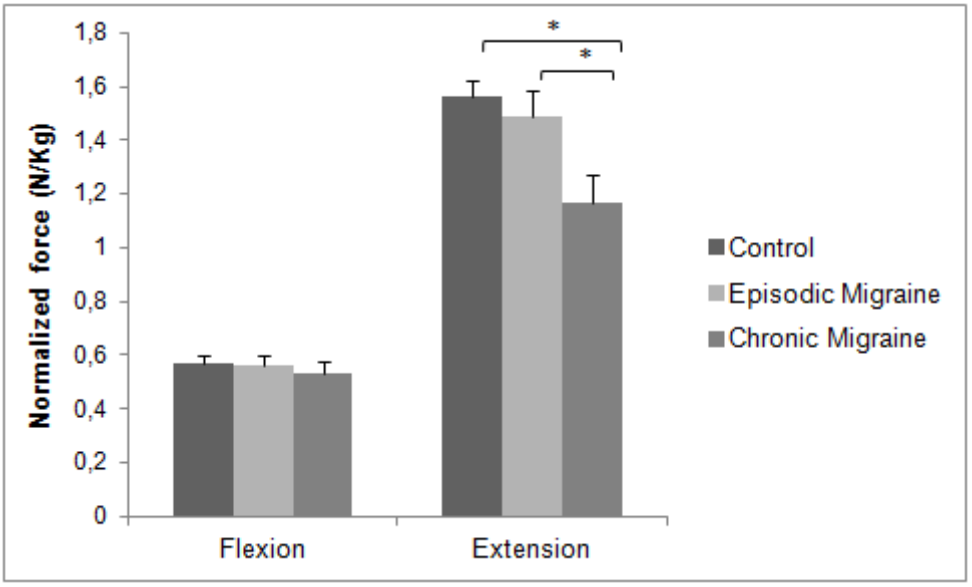
Extension
Control
Episodic Migraine
Chronic Migraine

Figure 1


Normalized force (N/Kg)
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*
*
Flexion
Extension
Control
Episodic Migraine
Chronic Migraine

Figure 2

3.5 Article 5- Published at Clin J Pain 2017;33(3):238-245

Active Trigger Points in the Cervical Musculature Determine the Altered Activation of Superficial Neck and Extensor Muscles in Women With Migraine

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Objective: Previous studies have demonstrated the presence of active trigger points (TrPs) in women with migraine reproducing their headache attacks. No study has investigated whether these TrPs can alter muscle function in the cervical spine in migraine. Our objective was to analyze differences in the activation of superficial neck flexor and extensor muscles in women with migraine considering the presence of active TrPs in the splenius capitis (SC), the upper trapezius (UT), and the sternocleidomastoid (SCM) muscles.

Methods: Surface electromyography was recorded from the superficial flexor (SCM and anterior scalene) and the extensor (SC) increase muscles bilaterally as participants performed a staged task of cranio-cervical flexion (CCF; 5 contractions representing a progressive in the CCF range of motion) in 70 women with migraine. They were stratified according to the presence or the absence of active TrPs in the SCM, the SC, or the UT musculature. A comparison of normalized root mean square (RMS) values was conducted with 2x 5 analysis of covariance with the task level as the within-subject variable, group stratified by active TrPs as the between-subjects variable and the presence of neck pain as a covariable.

Results: All patients exhibited active TrPs in their cervical muscles, which reproduced their migraine. Women with migraine exhibiting active TrPs in the SCM ($P < 0.01$), the UT ($P < 0.05$), or the SC ($P < 0.05$) muscles had lower normalized RMS values of their superficial neck flexors than those without active TrPs in the same muscles. In addition, individuals exhibiting active TrPs in the SC and the UT (both, $P < 0.05$) muscles had higher normalized RMS values in the SC muscle than those without active TrPs in the same muscles.

Conclusions: The presence of active TrPs in the cervical musculature determines an altered activation of superficial neck and extensor muscles during low-load, isometric CCF contractions in women with migraine.

Key Words: migraine, cranio-cervical flexion test, trigger points, electromyography

Received for publication February 10, 2016; accepted May 15, 2016

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L.L.F. received grant from the São Paulo Research Foundation (FAPESP) (process number 2012/22245-2).

The authors declare no conflict of interest.

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Clin J Pain DOI: 10.1097/AJP.0000000000000390

Migraine is a disabling primary headache described as a chronic disorder with recurrent attacks. Migraine has a worldwide prevalence ranging from 5% to 12%.[1]Although migraine pain is mostly perceived in the ophthalmic distribution of the trigeminal nerve, neck pain is also a prevalent concomitant symptom in this pop-ulation.[2–4] In fact, approximately 76% of the migraine patients also report the presence of neck pain,[5] which can occur as a premonitory manifestation, during the headache phase or even in the interictal period.[6]

It has been suggested that the association between neck pain and migraine occurs because the trigeminal-cervical convergence provides an anatomic and neurophysiological path for interaction through the convergence of cervical and trigeminal nociceptive afferents in the trigeminocervical nucleus caudalis.[7,8] In addition, central sensitization presenting in most individuals with migraine may facilitate neck pain and related disorders.[9] The presence of neck pain has a negative influence on migraine by reducing the pharmacological treatment response.[10,11]

Experience of pain or even the anticipation of pain may promote a variety of motor control changes involving the redistribution of activity within and between muscles.[12] Previous studies investigating neck muscle activity in patients with migraine revealed varying results. For instance, during maximal voluntary isometric contractions of the neck musculature, an increased coactivation of antagonist muscles was observed in girls[13] and women with either episodic or chronic migraine,[14] whereas the maximal strength seems to be affected only in women with chronic migraine.[14] However, during low-load tasks such as the cranio-cervical flexion test (CCFT), no significant differences in the activation of superficial neck flexors were observed in individuals with migraine.[15,16] These varying results may reflect the different tasks examined (strength vs. motor control), but may also suggest that changes in the activation of the cervical musculature are present only in some patients with migraine, rather than being unequivocally associated with most migraine patients. Interestingly, these previous studies have not taken into account the presence of trigger points (TrPs) in the neck musculature. Yet, it is well described that patients with migraine exhibit more active TrPs, those which reproduce the migraine attack when stimulated,[17] in the cranio-cervical muscles compared with individuals without headache.[18,19] The presence of TrPs has been associated with motor disturbances as they can promote fatigue, altered coordination, and an altered pattern of intramuscular activity.[20–22] No previous study has investigated the potential influence of active TrPs in the neck musculature on electromyographic activity of superficial neck flexor and extensor muscles during CCFT in individuals with migraine. Therefore, the aim of the current study was to investigate differences in the activation of superficial neck

flexor and extensor muscles during CCFT in migraine patients considering the presence of active TrPs in the splenius capitis (SC), the upper trapezius (UT), and the sternocleidomastoid (SCM) muscles. We hypothesized that the presence of active TrPs in the cervical musculature would be associated with an altered activity of the superficial neck muscles.

METHODS

Participants

Patients with migraine without aura were recruited from an urban regional hospital between November 2014 and October 2015. Patients were diagnosed following the third edition of International Headache Society criteria by an experienced neurologist.[23] Migraine features including the location, the quality of pain, years with disease, the frequency and the intensity of attacks, family history, and medication intake were collected as the clinical history. No abnormalities were detected in routine blood analyses with ESR or urine analyses. An x-ray examination of the skull and the cervical spine and a computed tomographic scan or magnetic resonance imaging of the head were invariably performed, and did not show any structural lesion. They were excluded if they presented any of the following criteria: (1) other concomitant primary or secondary head ache; (2) medication overuse headache; (3) a history of cervical or head trauma (ie, whiplash); (4) pregnancy; (5) a history of cervical herniated disk or cervical osteoarthritis on medical records; (6) any systemic degenerative disease for example, rheumatoid arthritis, lupus erythematous; (7) diagnosis of fibromyalgia syndrome; (8) anesthetic block in the past 3 months; or (9) receiving physical therapy intervention in the head and neck in the previous 6 months. A careful clinical examination of each participant was conducted to determine inclusion and exclusion criteria.

All participants signed the informed consent form before their inclusion in the study. The local Ethics Committee of Hospital Rey Juan Carlos (HRJ 07/14) approved the study design.

Clinical Measures

Clinical data including years with migraine, the migraine frequency (d/mo), the intensity of pain attacks (numerical pain rate scale, 0 to 10), headache duration (hours per attack), and the presence of self-reported neck pain, including report of the frequency, the intensity, and years with neck pain, were collected systematically.

CCFT

CCFT is a low-load graded test of deep cervical flexor muscle performance with 5 progressive stages guided by a pressure biofeedback unit (Stabilizer, Chattanooga Group Inc., South Pacific, Fig. 1). It is performed with the patient in the supine position, with the head and neck in a neutral position. The pressure biofeedback unit is placed behind the patient's neck in the suboccipital region, with an initial inflation pressure of 20 mm Hg.[24]

First, participants were familiarized with the test. They were instructed to perform a gentle head-nodding action of CCF over 5 incremental stages of increasing range of motion (2 mm Hg each stage) and each stage was maintained for 10 seconds. Head extension, head lift, or opening the mouth, described as compensations strategies,[24] were discouraged at familiarization time.

After the familiarization phase, a rest period of 1 minute was permitted. Participants then performed CCFT by holding each target level for 10 with 30 seconds' rest between levels. During the holding phase, surface electromyography (EMG) of selected neck flexors and extensor muscles was acquired. The full CCFT was repeated twice with a 15 minutes' rest in between. All participants per-formed all CCFT levels, and compensatory strategies were not controlled during the formal test. The CCFT examination was conducted by an assessor blinded to the presence or the absence of TrPs.

EMG Acquisition and Processing

After gentle skin abrasion using an abrasive paste, bipolar surface EMG was recorded with pairs of electrodes positioned 20 mm apart (Ambu-Blue Sensor N-50-K/25) and fixed firmly with an adhesive tape bilaterally over the following cervical muscles: (1) the sternal head of the SCM muscle: over the muscle belly at 1/3 of the distance from the sternal notch to the mastoid process[25]; (2) the anterior scalene (AS): over the muscle belly parallel to the clavicular head of the SCM[25]; and (3) the SC muscle: over the muscle belly at the C2-C3 level between the uppermost parts of the SCM and the UT muscles.[26] The reference electrode was placed on the

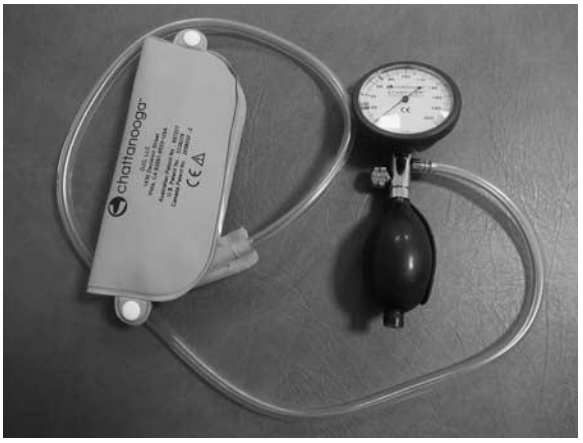

FIGURE 1. The pressure biofeedback unit (Stabilizer, Chattanooga Group Inc., South Pacific) used during the cranio-cervical flexion text.

wrist of the participants. Myoelectric signals from the SCM, the AS, the SC, and the UT muscles were amplified by 5000 (EMG16, 16-channel amplifier, LISiN- OT Bioelettronica, Torino, Italy), filtered (3 dB band- width, 10 to 450 Hz), sampled at 2048 Hz, and converted to 12-bit digital samples.

A customized MATLAB code (The Mathworks, Natick, MA) was used for data processing. EMG raw signals were band-filtered at 20 to 400 Hz (fourth order Butterworth) and the average root mean square (RMS) was calculated from each 10-second contraction. Neck flexor and extensor RMS values were normalized and expressed as a percentage of the maximum RMS value during a reference voluntary contraction. The reference activity for superficial neck flexors was a head-lift task, and for superficial neck extensors was head extension against the table in the supine position. For analysis purposes, mean RMS values were averaged over the 2 repetitions for each CCFT stage. Finally, the mean of the right and the left sides for each muscle were considered in the analysis for all CCFT stages.

TrP Identification

Screening for TrPs was performed by an assessor with6 years of experience in TrP diagnosis. The SCM, the SC, and the UT muscles were assessed bilaterally as TrPs in these muscles referred pain to the head mimicking migraine.[18,19] TrP diagnosis was performed according the following criteria[17]: (1) the presence of a palpable taut band in the muscle; (2) the presence of a painful spot in the taut band; (3) local twitch response on snapping palpation of the taut band; and (4) reproduction of the referred pain during manual examination. TrP diagnosis was conducted using snapping palpation (first to locate the taut band, and then

moving the thumb tip back and forth to roll the underlying fibers) to induce a local twitch response, and flat palpation (placing the padded aspect of the thumb on the painful spot and applying pressure against the underlying tissue or bone) to induce the referred pain. Participants were evaluated during interictal migraine states and pain-free states, and when at least 1 week had elapsed since the last migraine attack to avoid migraine related allodynia. TrPs were considered active when the referred pain elicited during manual examination reproduced the migraine attack features that the patient usually suffered from, and, therefore, the pain was recognized as a familiar pain.[17] Patients were classified as having active TrPs when they had TrPs reproducing their migraine attack in at least 1 muscle, either on the left or the right side.

Statistical Analysis

Data were analyzed with SPSS software version 20.0(SPSS Inc., Chicago, IL). Means and 95% confidence intervals (CI) were calculated for the clinical variables. Patients were stratified according to the presence of active TrPs in the SCM, the SC, and the UT muscles separately. The comparison for the normalized RMS values was conducted with a 2 5 analysis of covariance with the CCFT stage (22, 24, 26, 28, and 30 mm Hg) as the within-subject 61 variable, stratification (presence or absence of active TrPs) as the between-subject variable, and the presence of neck pain as the covariate. Separate analysis of covariances were conducted depending on the muscle affected by active TrPs (SCM, SC, and UT). The statistical analysis was conducted at 95% CI level. A P-value <0.05 was considered statistically significant.

RESULTS

Clinical Features of the Sample

From 100 eligible participants with migraine who accepted to participate, 30 were excluded for the following reasons: other comorbid headaches (n = 15), receiving anesthetic block (n = 6) or botulinium toxin A (n = 6) in the past 3 months, and reporting previous head or neck trauma (n = 3). Finally, 70 women, mean age 42 ± 12 years, with episodic migraine without aura were included. A total of 58 women (83%) self-reported neck pain. All women exhibited active TrPs reproducing their migraine attacks. The mean ± SD number of active TrPs for each patient with migraine was 3.0 ± 1.5. The UT muscle was the most affected by active TrPs in our sample (n = 41, 59%). Table 1 summarizes demographic and clinical data

of the total sample. The clinical status of patients was not dependent on the presence of TrPs in each cervical muscle (Table 2).

TABLE 1. Clinical and Demographic Characteristics of Women With Migraine

	Mean	95% CI	
		Lower	Upper
Migraine (n = 70)			
Age (y)	42	39	45
BMI (kg/cm^2)	24.2	23.2	25.1
Migraine features			
Years with migraine	19.3	16.1	22.6
Intensity (NPRS, 0-10)	8.1	7.7	8.6
Frequency (d/mo)	10.2	8.3	12.1
Duration (h/attack)	24.4	19.6	29.2
Neck pain			
No. patients (n [%])		58 (83)	
Time onset (y)	13.0	9.9	16.0
Intensity (NPRS, 0-10)	6.6	6.2	7.0
Active trigger points			
Sternocleidomastoid (n [%])		36 (52)	
Upper trapezius (n [%])		41 (59)	
Splenius capitis (n [%])		29 (41.5)	

BMI indicates body mass index; CI, confidence interval.

Neck Flexor Activity and TrPs

Normalized RMS values for the SCM and the AS muscles during the 5 stages of CCFT in patients with active TrPs in the SCM, the UT, and the SCs are shown in Figures 2–4. There was an increase in the EMG amplitude of SCM and AS with progressive stages of the test independent of the presence of active TrPs in the SCM muscle (SCM: $F = 16.57$, $P < 0.001$; AS: $F = 15.35$, $P < 0.001$), the UT muscle (SCM: $F = 12.59$, $P < 0.001$; AS: $F = 16.54$, $P < 0.001$), or the SC muscle (SCM: $F = 16.15$, $P < 0.001$; AS: $F = 10.18$, $P < 0.001$). Women

with migraine exhibiting active TrPs in the SCM muscle (SCM: F = 10.307, P = 0.002; AS: F = 7.169, P = 0.009), the UT muscle (SCM: F = 5.19, P = 0.026; AS: F = 4.491, P = 0.044) or the SC muscle (SCM: F = 7.852, P = 0.007; AS: F = 6.437, P = 0.018) showed lower normalized RMS values of their superficial neck flexors than those without active TrPs in the same muscles (Figs. 2–4). The presence of neck pain did not influence the results (SCM: P > 0.253; AS: P > 0.356).

TABLE 2. Clinical and Demographic Characteristics of Women With Migraine According to the Presence or the Absence of Active Trigger Points (TrPs)

	Active TrPs SCM (N = 36)		Active TrPs UT (N = 41)		Active TrPs SC (N = 29)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Neck pain						
No. patients (n [%])	31 (85)		33 (80)		24 (82)	
Time of onset (y)	11.8	(7.3-16.2)	11.9	(7.9-16.2)	13.8	(7.8-18.4)
Intensity (0-10)	5.9	(5.0-6.9)	5.6	(4.7-6.6)	5.9	(5.0-7.0)
Migraine features						
Years with migraine	19.3	(14.7-23.9)	18.6	(14.5-22.8)	19.6	(14.8-24.5)
Intensity (NPRS, 0-10)	8.2	(7.6-8.8)	8.2	(7.6-8.7)	8.1	(7.5-8.8)
Frequency (d/mo)	10.2	(7.3-13.1)	10.4	(7.7-13.1)	9.3	(6.3-12.9)
Duration (h/attack)	25.2	(17.3-29.1)	25.8	(19.5-32.0)	25.0	(17.8-32.1)

CI indicates confidence interval; SC, splenius capitis; SCM, sternocleidomastoid; UT, upper trapezius.

Neck Extensor Activity and TrPs

Normalized RMS values for SC muscle during the 5 stages of CCFT in patients with active TrPs in the SCM, the UT, and the SC muscles are shown in Figure 5. There was also an increase in the EMG amplitude of SC with progressive stages of the test independent of the presence of active TrPs in either the SCM ($F = 4.41$, $P = 0.039$), UT ($F = 4.591$, $P = 0.045$) or the SC ($F = 11.176$, $P < 0.001$) muscles. In contrast to the results for the flexor muscles, the results revealed higher normalized RMS values in the SC muscle in women with migraine exhibiting active TrPs in 33 the SC ($F = 4.05$, $P = 0.046$) and the UT ($F = 4.014$, $P = 0.046$) muscles (Fig. 5) compared with those without active TrPs in the same muscles. No significant differences were observed for normalized RMS values in the SC in 37 patients with active TrPs in the SCM muscle ($F = 0.290$,$P = 0.592$, Fig. 5). The presence of neck pain (SC: $P > 0.213$; UT: $P > 0.293$) did not influence the results.

DISCUSSION

Women with migraine exhibiting active TrPs in the SCM, the SC, and the UT muscles had lower activation of their superficial neck flexors, that is, SCM and AS, during low-load CCF contractions. In addition, the presence of active TrPs in the superficial neck extensors, that is, SC and UT, determined increased activation of the SC muscle during CCF contractions.

It is well known that noxious stimulation of a muscle, for example, with experimental muscle pain through intramuscular injection of hypertonic saline, induces a temporary decrease in the EMG amplitude of the painful muscle together with compensatory strategies within the same muscle[27,28] or across synergistic muscles.[29–31] It may be speculated that a long-lasting nociceptive irritant, such as an active TrP, also induces the inhibition of the

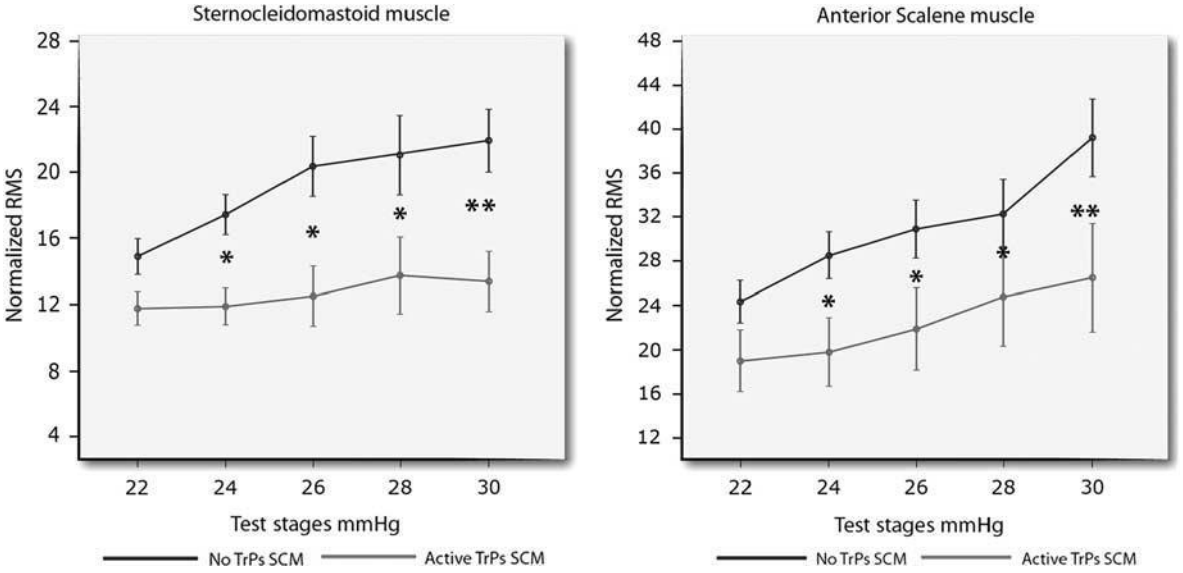

FIGURE 2. Normalized root mean square (RMS) values for the sternocleidomastoid and the anterior scalene muscles for the five stages of the cranio-cervical flexion test depending on the presence or the absence of active trigger points (TrPs) in the sternocleidomastoid (SCM) muscle (SCM-yes, n = 36/no, n = 41). Values for the left and the right muscles have been averaged. Data are expressed as means and SEM. *P < 0.05; **P < 0.01.

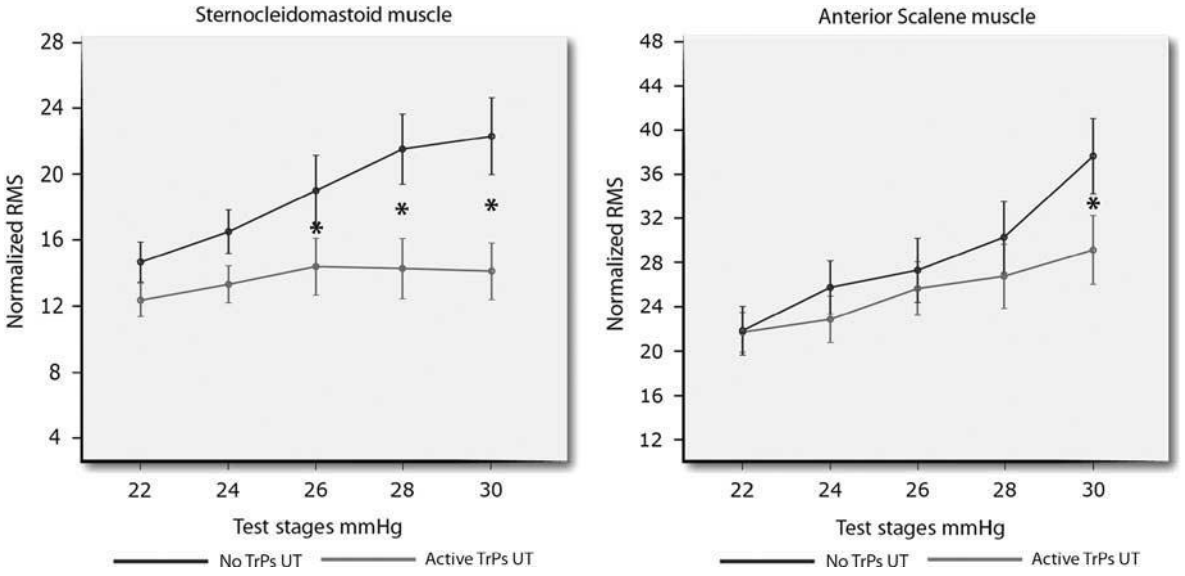

FIGURE 3. Normalized root mean square (RMS) values for the sternocleidomastoid and the anterior scalene muscles for the 5 stages of the cranio-cervical flexion test depending on the presence or the absence of active trigger points (TrPs) in the upper trapezius (UT) muscle (UT-yes, n = 41/no, n = 29). Values for the left and the right muscles have been averaged. Data are expressed as means and SEM. *P < 0.05; **P < 0.01.

painful muscle when activated. This knowledge may explain the reduced activation of the SCM and the AS muscles in individuals with active TrPs in the same musculature. Interestingly, reduced activation of SCM and AS was also noted in women with active TrPs in the SC or the UT muscles, which implies that the altered muscle strategy is not necessarily due to pain-induced inhibition locally within the muscle. The observation of reduced activation of SCM and AS during CCFT in the women with migraine and active TrPs is in

contrast to observations in people with primary neck disorders, including cervicogenic headache.[15,16]

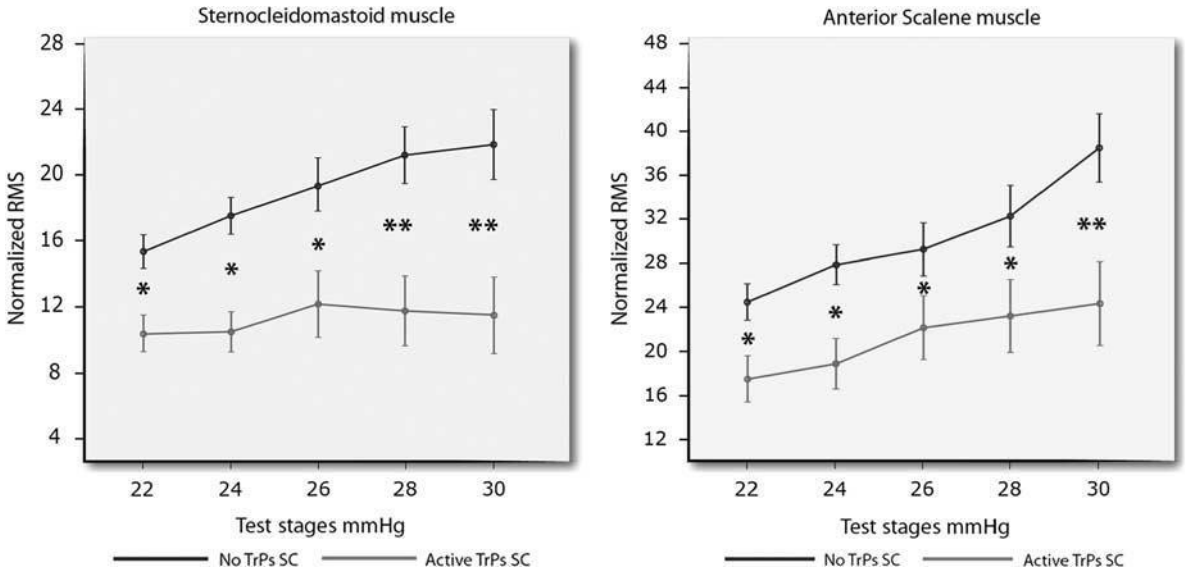

FIGURE 4. Normalized root mean square (RMS) values for the splenius capitis muscle for the 5 stages of the cranio-cervical flexion test depending on the presence or the absence of active trigger points (TrPs) in the splenius capitis (SC) muscle (SC-yes, n = 29/no, n = 41). Values for the left and the right muscles have been averaged. Data are expressed as means and SEM. *P < 0.05; **P < 0.01.

Rather, people with cervical spine disorders show a higher activity of the SCM and the AS muscles during CCFT, which has been shown to be an indicator of poor performance of the deep neck flexor muscles, that is, the longus colli and the longus capitis.[32,33] However, migraine is a primary headache mainly associated with brain dysfunction with deficient regulation of the excitatory-inhibitory balance during cortical activity, leading to trigemino-vascular sensitization. Thus, although individuals with migraine usually suffer from concomitant neck pain,[5] they do not have a primary neck pain disorder, which would explain these contrasting results. Nevertheless, we observed that the presence of active TrPs within the cervical musculature implies different activation of the neck flexor muscles compared with those without active TrPs in the same muscles.

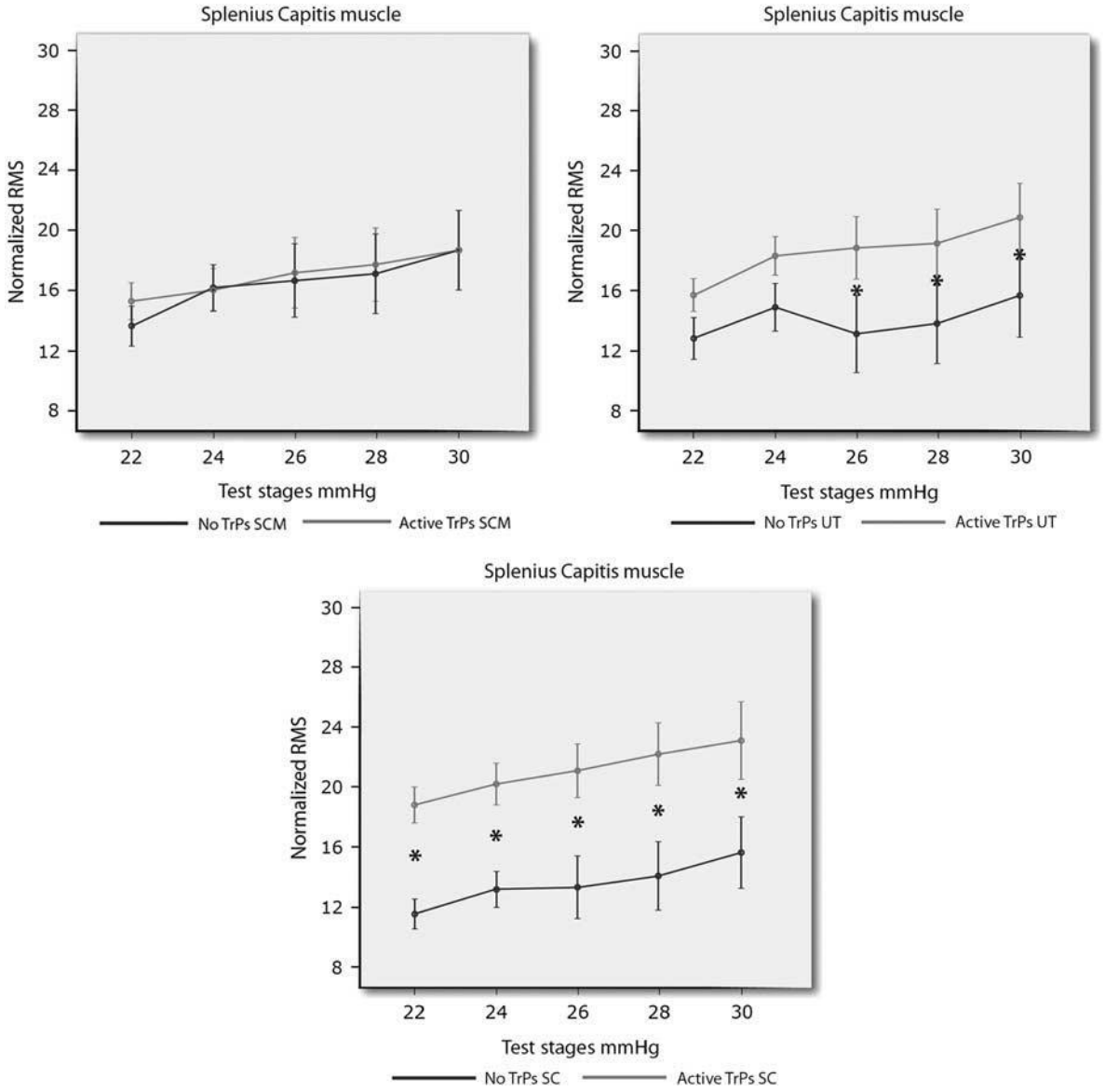

FIGURE 5. Normalized root mean square (RMS) values for the splenius capitis muscle for the 5 stages of the cranio-cervical flexion test depending on the presence or the absence of active trigger points (TrPs) in the sternocleidomastoid (SCM-yes, n = 36/no, n = 41), the upper trapezius (UT-yes, n = 41/no, n = 29), or the splenius capitis (SC-yes, n = 29/no, n = 41) muscles. Values for the left and the right muscles have been averaged. Data are expressed as means and SEM. *P < 0.05; **P < 0.01

Interestingly, differences in muscle activation were associated with the presence or the absence of active TrPs, but not related to the presence of neck pain in our study. During tasks with low mechanical demands, performance can be maintained despite pain, also through the modification of antagonist musculature activity.[30,34] Indeed, one theory of the motor adaption to pain indicates that muscle pain induces reorganization of the motor strategy characterized by reduced activity of agonist muscles and increased activity of antagonist muscles (pain adaptation theory).[35] The current work supports the observation of increased antagonist muscle activity as increased SC muscle activity was noted when active TrPs were present within the SC or the UT muscles. In support of the current findings, individuals with chronic,

but not episodic, migraine exhibit higher activity of their superficial neck extensors (ie, SC muscle) during low-load, isometric CCF contractions compared with non headache individuals (unpublished observations), and women with chronic tension-type headache also show greater coactivation of antagonist muscles (ie, the SC muscle) during isometric neck flexion contractions compared with headache-free individuals.[36] Thus, increased coactivation of the antagonist musculature appears to be a common feature in people with headache. Results from the current study suggest that increased antagonist muscle coactivation is even more likely in individuals with active TrPs.

Overall, the observation that TrPs are associated with changes in the activation of agonist and antagonist muscles [13] is consistent with earlier findings. Ibarra et al[22] observed increased muscle activity at latent TrPs in an antagonist muscle (ie, posterior deltoid muscle) during a shoulder flexion task. Lucas et al[37] found that the presence of latent [17] TrPs impaired the recruitment or the timing of muscle activation when performing active joint movement, and Ge et al[20] found that the presence of latent TrPs induced incoherent muscle activation patterns in the synergist musculature during muscle contractions. However, these studies included latent TrPs, but not active TrPs, which limit the clinical relevance of their data as latent TrPs are not related to clinical pain complaints. Our study is the first one showing that the presence of active TrPs was associated with a different pattern of agonist and antagonist muscle activation in patients with headache. Our finding has potential implication for clinical practice. As the presence of active TrPs in the cervical musculature is related to an altered pattern of neck muscle activation, it would be recommended that clinicians first treat these TrPs before starting any therapeutic exercise program targeting normalizing motor control disturbances observed in these patients.

Although the study expands the current knowledge on changes in muscle behavior in individuals with migraine, potential limitations should be recognized. First, we included only women with migraine, and therefore, we do not know whether the same results would be observed in men. Second, we included a single low-load CCF task for investigating muscular activity, but this task does not necessarily represent muscle demands during daily life activities. Third, psychological features, for example, fear of movement, were not measured and may have proven useful in understanding the mechanisms underlying the observed altered muscle behavior in people with migraine. Further, a control group of headache-free individuals was not included; thus, although we can confirm differences in the activation of the neck musculature between women with and without active TrPs in their cervical muscles,

we cannot confirm that the changed pattern of activation within the migraine group with active TrPs would be significantly different from that of asymptomatic people.

CONCLUSIONS

In the current study, all women with migraine exhibited active TrPs in the neck muscles reproducing their migraine attack. Women with migraine who have active TrPs in the cervical musculature show an altered pattern of neck muscle activation during a low-load cranio-cervical contraction compared with those without active TrPs in the evaluated muscle. Alterations of afferent input (ie, painful stimulus induced by active TrPs) appear to influence muscle activation at a multimuscular level.

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3.6 Article 6 – Submitted at PM&R

Elsevier Editorial System(tm) for PM&R Manuscript Draft

Manuscript Number:

Title: Head Posture is Associated with Higher Co-activation of the Cervical Neck Extensors during a Low-load Task in women with Chronic Migraine and Healthy Subjects

Article Type: Original Research

Keywords: Migraine; posture; cranio-cervical flexion test; surface electromyography.

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Head Posture is Associated with Higher Co-activation of the Cervical Neck Extensors during a Low-load Task in women with Chronic Migraine and Healthy Subjects

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Funding: This work was supported by Sao Paulo Research Foundation (FAPESP) [process number 2014/13103-5].

The material was not presented at an AAPM&R Annual Assembly.

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Head Posture is Associated with Higher Co-activation of the Cervical Neck Extensors during a Low-load Task in women with Chronic Migraine and Healthy Subjects

ABSTRACT

Objective: To correlate head and neck posture and superficial neck muscles activity during CCFT in women with migraine and healthy controls. **Design: A** cross-sectional study. **Setting: T**ertiary hospital. **Patients:** Fifty-two women with episodic migraine, 16 with chronic migraine and 23 healthy controls. **Methods**: Head and neck posture and superficial electrical activity of the cervical muscles was assessed. **Outcome Measures:** Head and neck posture was determined by assessing the cranio-vertebral (CV) angle and cervical lordosis angle, respectively. Surface electromyography signals were bilaterally recorded from sternocleidomastoid, anterior scalene, splenius capitis, and upper trapezius muscles as subjects performed the CCFT **Results:** Both migraine groups had significant increase in splenius capitis muscle activity at the last stage of CCFT ($F=4.687$; $P=0.012$) compared to controls. Groups did not differ regarding head and neck posture. Moderate correlations indicate that the more extended head posture, the higher the activity of upper trapezius and splenius capitis muscles is expected during the CCFT for chronic migraine ($-0.61<r<-0.65$, all $P<0.05$) and for control group ($-0.42<r<-0.52$; $P<0.05$). No significant correlation was found in the episodic migraine group and cervical lordosis also did not correlated with any muscle activity of all groups. **Conclusions:** An extended (forward) head posture was moderately correlated with an increase in electrical activity of superficial neck extensors muscles, particularly the upper trapezius, when acting as antagonist, during the performance of the CCFT in women with chronic, but not episodic, migraine.

Keywords: Migraine, posture, cranio-cervical flexion test, surface electromyography.

Head Posture is Associated with Higher Co-activation of the Cervical Neck Extensors during a Low-load Task in women with Chronic Migraine and Healthy Subjects

INTRODUCTION

Migraine is a disabling condition with significant impact in occupational and personal activities [1–3]. Among the several factors that can influence migraine clinical picture, neck pain has been found to be an important one. It seems that neck pain is highly prevalent in individuals with migraine (up to 80%), its presence may delay acute migraine treatment and higher neck-related disability is also associated with migraine chronification [4–7]. The association between migraine and neck symptoms is attributed to afferent convergences within the trigemino-cervical nucleus caudalis that is sensitized in migraine [8].

Patients with migraine presenting neck pain may also display altered patterns of cervical neuromuscular activation [9]. Changes in neuromuscular control as increased antagonist coactivation during maximal isometric neck muscles and increased activity of superficial cervical extensors during the craniocervical flexion test (CCFT) have been recently observed in migraineurs [10–12]. The fact that no differences in muscle activation of superficial neck flexors during CCFT performance [13,14] suggest that changes in motor performance in subjects with migraine may be distinct from those expected for primary neck disorders [15].

Controversy regarding the presence of altered head and neck posture in subjects with migraine discusses what pattern of alteration should be expected. In fact, some studies have reported that migraine patients exhibit forward head posture compared to healthy people, whereas others did not find such differences [13,16–18]. However, regardless of individuals with migraine exhibit an altered or normal posture, it is reasonable that altered head and/or neck posture can alter neck muscle function, e.g., due to changes in muscle fiber length [19]. In such scenario, Cagnie et al. (2008) found that head posture of healthy subjects did not significantly correlate with sternocleidomastoid (SCM) activity during the performance of CCFT. However, there is no available data regarding this correlation in people with migraine and even more the correlation of head and neck posture with activation activity of other neck muscles.

Therefore, the aim of this study was to investigate the association between head and neck posture and superficial cervical flexors (sternocleidomastoid, anterior scalene) and extensors (splenius capitis, upper trapezius) activity during performance of CCFT and to determine if there are differences in the relationships between individuals with migraine and healthy controls.

METHODS

Sample

Women with migraine aged between 18 and 60 years old were recruited from a tertiary hospital from November 2014 to October 2015. Participants were diagnosed according to the International Classification of Headache Disorders criteria, third edition (ICHD-3) down to third-digit level (code 1.1, 1.3) by a neurologist expert in headaches [2]. Migraine features including location, onset of migraine (years), the frequency (days/month) and intensity of migraine (numerical pain rate scale, 0-10), headache-family history and medication intake were collected. Exclusion criteria included any of the following: 1, other primary or secondary headaches, including medication overuse headache (MoH) accordingly to the ICHD3 criteria; 2, history of neck or head trauma; 3, pregnancy; 4, systemic medical disease, e.g., rheumatoid arthritis, or lupus erythematous; 5, diagnosis of fibromyalgia syndrome; or, 6, anesthetic blocks within the past 6 months. All participants signed the informed consent form before their inclusion in the study. The local Ethics Committee approved this cross- sectional study.

Further, a comparable healthy control group without headache history and no headache attack during the previous year was also recruited. Exclusion criteria for the control group were the same as the migraine groups. The evaluation was held when all patients were headache-free, and when one week had elapsed since the last migraine attack to avoid migraine-related allodynia. In those patients with chronic migraine, evaluation was conducted at least 3 days after a migraine attack. A clinician blinded to the subject's condition assessed all outcomes.

Head and neck posture

The head/neck posture was evaluated by a profile photograph of the cervical spine. Anatomical references were marked by adhesive markers fixed on the occipital bone and the spinous processes of the fourth and seventh cervical vertebrae [21,22]. Vertical reference

was provided by a metal plumb line positioned 33cm far from subjects. All photographs were obtained by the same technician using a digital camera with a lens of 23 mm (Samsung Lens WB350F®) positioned on a tripod at a distance of 4m from the subject and adjusted according to subject´s height.

Volunteers were photographed in standing upright and sitting positions without shoes. They were instructed to keep their habitual/comfortable position with their arms alongside the body and the head in a natural relaxed position looking forward [23]. For standing upright position, they were asked to keep feet at a comfortable distance apart, and camera lens center was placed at the half of height's subject [17]. For sitting position, the camera lens center was placed at the same distance of the height between ground and subject's acromioclavicular joint [18]. Photographs were analyzed using the CorelDraw-X7® software. Head posture was assessed by calculating the cranio-vertebral angle (CV), which is determined by the angle between the horizontal line and the line traced from the tragus to spinous process of C7: the smaller the CV angle, the higher the forward head posture [22]. Neck posture was assessed by determining the cervical lordosis angle: firstly, a horizontal line was traced from the C4 to the pumb line, and then two lines were traced converging to this first, one from occipital bone and other from the C7 vertebra. The angle formed at the intersection of these two last lines determines the lordosis angle (**Fig. 1**). A lower lordosis angle reflects higher cervical lordosis curvature [17,24].

Electromyography acquisition and processing

Bipolar surface electrodes were positioned 22mm apart (Ambu®-Blue Sensor N-50-K/25) after gentle skin abrasion using abrasive paste and shaving when necessary. Electrodes were placed at *1*, SCM muscle: over the muscle belly at1/3 of the distance from the sternal notch to the mastoid process orientated in the direction of the line that join these two structures [25]; *2*, Scalene muscle: over the muscle belly in the direction of fibres running parallel to the lateral boarder of the clavicular portion of SCM muscle at the same level of SCM electrode[25]; *3*, Splenius capitis muscle: over the muscle belly at C2-C3 level between the upper most parts of SCM and upper trapezius muscles and[26]; *4*, Upper trapezius muscle: median point of the distance between C7 spinal process and acromion (SENIAM). A ground electrode was placed around the subjects' wrist.

Myoelectric signals were acquired and amplified by 5000 (EMG16, 16-channel amplifier, LISiN-OT Bioelettronica®, Torino, Italy), filtered (-3dB bandwidth, 10-450 Hz), sampled at 2048 Hz, and converted to 12-bit digital samples. Raw signals were band-filtered a 20-400Hz (4th order Butterworth), and the average Root Mean Square (RMS) was

calculated from each 10s contraction by a customized MATLAB code (The MathworksTM, Natick, MA, USA). Electrical activity was normalized by the maximum RMS during the reference voluntary contraction and expressed as percentage. Reference activities consisted of head lift for superficial neck flexors, and head extension with manual resistance for neck extensors since submaximal normalization has demonstrated to reduce the variability and is considered to be more acceptable in patients with pain than maximal contraction normalization procedure [28]. Both contractions were performed with participants in a supine position, sustained for 10sec and repeated 2 times after the CCFT performance. Average from two repetitions of left and right neck
muscles RMS values were used in the analysis.

Cranio-cervical flexion test

The CCFT is commonly applied to determine deep neck flexor muscle performance during a low-load task with 5 progressive stages (22 to 30mmHg) guided by a pressure biofeedback unit (PBU) (Stabilizer®, Chattanooga Group Inc. USA) [29]. An increase in the activity of superficial cervical flexors, i.e., SCM and anterior scalene, is considered a consequence of deficient function of deep cervical flexors, i.e., longus colli and longus cervicis muscles [30].

Volunteers were positioned in supine, with the head and neck in neutral, and the PBU was placed at the suboccipital area behind the subject's neck. The initial PBU's inflation pressure was 20mmHg and a progressive incremental of a 2mmHg scale was applied. Habituation with the test was performed first: subjects were asked to perform a gentle head nodding action of CCF and discouraged to use compensations strategies such as head lift, head extension or opening the mouth. At this phase, subjects needed to reach the target level and return to the neutral position. To acquire the myoelectrical signal, each stage target was maintained for 10sec and repeated two times with a 30sec resting interval between them.

Statistical analysis

Data were summarized by means, standard deviation or 95% confidence interval. Sample characteristics and normalized RMS were compared among the groups (chronic migraine, episodic migraine or healthy controls) by an analysis of variance (ANOVA) applying Bonferroni´s test as a *post-hoc*. Correlations between the CV, lordosis angle and normalized RMS for each neck muscle at all CCFT stages were calculated by the Pearson´s correlation coefficient (r) separately for chronic migraine, episodic migraine and healthy

controls. Correlations were classified as weak when $r < 0.3$; as moderated when r ranges from 0.3 to 0.7 and as strong when $r > 0.7$[31]. All analysis was performed using the SPSS 20.0 software and adopting a significance level of 0.05.

RESULTS

From 122 eligible subjects with migraine who accepted to participated, 54 were excluded for the following reasons: co-morbid headaches (n=19), receiving anesthetic block (n=8) botulinium toxin (n=5) or physical therapy (n=6); diagnosis of fibromyalgia (n=6); neck/head trauma (n=3); visual disturbance (n=4) or dizziness (n=3). Finally, 68 women, mean age: 43±11 years old, with migraine without aura were included. Fifty-two women (76%), mean age: 42±12 years, were classified as episodic migraine whereas the remaining 16 (24%), mean age: 44±13, were classified as chronic migraine. In addition, a comparable group of 23 healthy women, age: 44±12 years, was also included. No significant differences in demographic variables were observed among the 3 groups, except for the frequency of headache ($P<0.001$) and the presence of neck pain ($P<0.01$). **Table 1** shows clinical and demographic data of each group.

There were no significant differences in head posture in either sitting ($F=1.388$; $P=0.255$) or standing ($F=1.675$; $P=0.193$) positions among individuals with episodic or chronic migraine and healthy controls. Similarly, no significant differences were found among groups for cervical lordosis in sitting ($F=1.659$; $P=0.196$) and standing upright ($F=0.684$; $P=0.508$) positions (**Fig. 2)**.

The ANOVA revealed that both migraine groups exhibited increased activity of the splenius capitis muscle, when acting as antagonist, as compared to healthy controls at CCFT stage of 30mmHg ($F=4.687$; $P=0.012$). No further differences were observed on neck muscles activity during all stages of CCFT (**Fig. 3**).

No significant correlation was observed between CV or cervical lordosis angles and activity of superficial neck flexor or extensor muscles within the episodic migraine group (**Table 2**). In the chronic migraine group, the CV angle in sitting position showed significant negative moderate correlations with normalized RMS of the upper trapezius muscle at all CCFT stages ($-0.61<r<-0.65$, all $P<0.05$). Further, the CV angle within the standing position also showed significant and negative correlations with normalized RMS of the upper trapezius muscle at 22, 24, 28 and 30mmHg stages ($-0.50<r<-0.56$, all $P<0.05$): the lower the CV, i.e., the greater the forward head posture in either sitting or standing positions, the

higher activity of upper trapezius muscle, acting as antagonist, during the majority stages of the CCFT (**Table 2**). The cervical lordosis angle did not exhibit any significant correlation with activity of superficial neck flexors or extensor muscles within the chronic migraine group (**Table 2**).

In the healthy control group, significant moderate and negative correlations were observed between the CV angle and upper trapezius muscle activity in the first stage ($r=-0.44$; $P=0.040$) and with splenius capitis muscle activity in the last three stages of the CCFT ($-0.42<r<-0.52$; all $P<0.05$): again, as the head becomes more forward, the superficial extensors activity, when acting as antagonists, is higher (**Table 2**). Similarly, the cervical lordosis angle did not exhibit any significant correlation with the activity of superficial neck flexors or extensor within the control group (**Table 2**).

DISCUSSION

The current study found that an extended (forward) head posture was moderately correlated with an increase in electrical activity of superficial neck extensor muscles, particularly the upper trapezius, when acting as antagonist, during the performance of the CCFT in women with chronic, but not episodic, migraine. This association was also observed in healthy controls without history of headache.

We did not find differences in superficial neck flexors activity during the CCFT, which is in agreement with previous data [12–14]. Further, women with migraine displayed significant increased activity of the splenius capitis muscle, when acting as antagonist, during the last stage of the CCFT suggesting previous hypothesis that motor control changes seen in migraineurs do not match the pattern of activation expected for subjects with primary neck pain mainly characterized by an increased activity of the superficial neck flexors [12,15]. Additionally, we did not also observe differences in head/neck posture between women with migraine and healthy women, again in agreement with previous studies [13,32].

To the best of the author's knowledge, there is only one previous study analyzing the correlation of head posture and neck muscle activity during performance of CCFT[20]. This study was conducted in healthy subjects and no significant correlations between head posture and SCM muscle activity could be demonstrated [20]. Our results agree with this study since we did not also find any association between head or neck posture with the activity of superficial neck flexors, i.e., SCM and anterior scalene, in neither healthy people

nor patients with migraine. This may be related to the fact that individuals with migraine did not display altered activity of the superficial neck flexors as compared to healthy people. We do not know if correlation between these variables may be present in patients with primary neck pain; but current data suggest that at least for migraineurs suffering concomitant neck pain, the lack of significant correlation between head/neck posture and superficial cervical flexors activity still occurs.

The novelty of our study was to add the analysis of superficial neck extensors acting as antagonists, during the CCFT. We found moderate correlations between head posture and superficial neck extensor muscles, particularly the upper trapezius muscle, suggesting that a more extended (forward) head posture was correlated with an increase activity in the upper trapezius, when acting as antagonist, in women with chronic, but not episodic, migraine during the performance of the CCFT. Similarly, a more extended head posture was also correlated with an increased activity of splenius capitis and upper trapezius muscles in healthy subject. Our findings differ from those previously reported by Lee et al. 2015. This study associated a forward head posture with a reduced activity of neck muscles during head protraction and retraction movements. It is possible that differences on the task, differences in populations, or the method determining forward head posture may justify discrepancies between studies.

To determine the mechanisms underlying the association between head posture and an increased activity of superficial neck extensors is beyond the scope of the current study; however, current results have some potential implications for clinical practice in relation to assessment of the cervical spine for applying better therapeutic interventions for patients with migraine. For instance, our study suggests that motor control exercise programs of the cervical spine should target both superficial neck flexors and extensors in patients with migraine. In addition, proper head posture should be achieved during the exercises for avoiding over-activation of the superficial neck extensors. Finally, the application of manual therapies for decreasing muscle activity of the upper trapezius muscle can also be applied before staring the exercise programs. Nevertheless, since we did not find differences on head and neck posture between women with migraine and healthy women and no correlation was shown between head posture and splenius capitis muscle activity during the CCFT in subjects with migraine; we should not attribute the higher activation of the splenius capitis muscle, when acting as antagonist, observed in both migraine groups to differences in posture. This motor control change observed in subjects with migraine may be a distinct adaptation as a consequence of the imbalance of the central pain modulation or

even be a consequence of other factors not included in the current study as previously suggested [12]. We proposed that head and neck posture may act as a contributing factor for muscle co-activation, but in any case, as the main cause.

Although this is the first study investigating the influence of posture in muscle activity of the superficial neck flexors and extensors in migraine, we should recognize some potential limitations. First, we included women recruited from a tertiary headache centre. Although migraine is more prevalent in women [34], we do not know if the same results would be observed in community-based populations or in men. Second, there are other aspects, such as fear to movement, that have not been included in this study that could be correlated to neck muscle activity.

CONCLUSIONS

This study found that women with migraine exhibited increased activation of the splenius capitis muscle, acting as antagonist during the performance of CCFT compared to healthy women. No significant differences in head and/or neck posture were observed between patients and controls. An extended (forward) head posture was correlated with an increase in electrical activity of superficial neck extensor muscles, particularly the upper trapezius muscle, when acting as antagonist, during the performance of the CCFT in women with chronic, but not episodic, migraine. This association was also observed in healthy controls without history of headache.

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FIGURE LEGENDS

Figure 1: Assessment of the cranio-vertebral (left) and cervical lordosis (right) angles.

Figure 2: Assessment of head and neck posture (mean and standard error) in women with migraine (episodic or chronic) and healthy women.

Figure 3: Normalized root mean square (RMS) of neck muscles during the five stages of cranio-cervical flexion test for episodic migraine (n=52), chronic migraine (n=16) and healthy controls (n=23).
* Differences between episodic and chronic migraine ($P<0.05$)

Table 1: Demographic and clinical pain features of migraine and healthy control groups

	Healthy Controls (n=23)	Episodic Migraine (n=52)	Chronic Migraine (n=16)
Age (years)	44 (39 - 49)	42 (38 - 46)	44 (37 - 51)
Body mass index (kg/cm^2)	22.7 (21.5 - 24.3)	23.4 (22.4 - 24.4)	25.5 (22.5 - 28.4)
Migraine frequency (days/month)#	-----	6.2 (5.1 - 7.13)	21.9 (18.6 - 25.1)
Migraine intensity (NPRS; 0-10)	-----	8.2 (7.6 - 8.7)	8.0 (6.8 - 9.1)
Years with migraine	-----	18.3 (14.7 - 22.0)	24.1 (15.3 - 33.0)
Neck pain n (%)	7 (30%)	51 (98%)	16 (89%)
Years with neck pain	7.3 (1.6 - 13.0)	10.3 (6.8 - 13.8)	13.9 (5.5 - 22.3)
Neck pain intensity (NPRS, 0-10)	4.6 (2.7 - 6.4)	5.3 (4.5 - 6.1)	6.6 (5.1 - 8.0)

** Data are expressed in mean and confidence interval

Differences between episodic and chronic migraine groups (P<0.001)

Table 2: Correlation between head or neck posture according to cranio-vertebral (CV) and cervical lordosis (CL) angles and neck muscles activity during the performance of cranio-cervical flexion test (CCFT) in episodic migraine, chronic migraine, and healthy subjects (continued)

		Episodic Migraine (n=52)				**Chronic Migraine (n=16)**				**Healthy Controls (n=23)**			
		CV		**CL**		**CV**		**CL**		**CV**		**CL**	
CCFT	**RMS**	seated	upright	seated	upright	seated	upright	seated	upright	seated	upright	seated	upright
22 mmHg	SCM	0.15	0.22	0.16	0.17	-0.45	-0.14	-0.01	-0.24	0.20	0.08	0.21	-0.07
	Anterior Scalene	0.04	0.07	0.15	0.03	-0.24	-0,32	-0.16	-0.30	0.21	0.16	0.25	0.09
	Splenius Capitis	0.12	0.16	-0.12	0.03	-0.23	-0.10	-0.02	-0.24	-0.28	0.02	0.02	0.36
	Upper Trapezius	-0.16	0.04	-0.16	-0.18	-0.63**	-0.50*	-0.28	0,08	-0.44*	-0.27	0.01	0.12
24 mmHg	SCM	0.02	0.09	0.12	0.08	-0.47	-0.28	0,01	-0.28	0.23	0.07	0.22	-0.08
	Anterior Scalene	-0.10	-0.05	0.03	-0.04	-0.47	-0.49	-0.06	-0.29	0.13	0.13	0.17	0.11
	Splenius Capitis	0.11	0.14	-0.12	0.01	-0.23	-0.09	0.01	-0.21	-0.20	0.12	0.18	0.05
	Upper Trapezius	-0.22	-0.03	-0.17	-0.21	-0.63**	-0.51*	-0.28	0.09	-0.25	0.14	0.28	0.40
26 mmHg	SCM	0.06	0.11	0.05	-0.07	-0.47	-0.30	-0.17	-0.28	0.25	0.15	0.29	-0.004
	Anterior Scalene	0.03	0.06	0.05	-0.06	-0.16	-0.28	-0.18	-0.25	0.07	0.17	0.23	0.25
	Splenius Capitis	0.11	0.11	-0.12	-0.08	-0.23	-0.06	-0.01	-0.14	-0.42	-0.51*	-0.23	-0.09
	Upper Trapezius	-0.17	-0.01	-0.18	-0.21	-0.61*	-0.49	-0.25	0.11	-0.41	-0.25	0.04	0.14

SCM= sternocleidomastoid; * P<0.05; ** P<0.01

Table 2: Correlation between head or neck posture according to cranio-vertebral (CV) and cervical lordosis (CL) angles and neck muscles activity during the performance of cranio-cervical flexion test (CCFT) in episodic migraine, chronic migraine, and healthy subjects.

		Episodic Migraine (n=52)				**Chronic Migraine (n=16)**				**Healthy Controls (n=23)**			
		CV		**CL**		**CV**		**CL**		**CV**		**CL**	
CCFT	**RMS**	seated	upright	seated	upright	seated	upright	seated	upright	seated	upright	seated	upright
28 mmHg	SCM	0.02	0.04	-0.02	-0.20	-0.43	-0.35	-0.23	-0.34	0.24	-0.02	0.10	-0.20
	Anterior Scalene	-0.05	-0.02	-0.03	-0.21	-0,20	-0.29	-0.03	-0.13	0.14	-0.01	0.03	-0.09
	Splenius Capitis	0.11	0.07	-0.14	-0.13	-0.19	-0.04	0.03	-0.08	-0.42*	-0.52*	-0.24	-0.09
	Upper Trapezius	-0.15	0.01	-0.16	-0.21	-0.65**	-0.53*	-0.32	0.02	-0.22	0.18	0.28	0.38
30 mmHg	SCM	-0.01	0.08	0.04	-0.05	-0.16	-0.12	-0.13	-0.08	0.28	0.01	0.13	-0.18
	Anterior Scalene	-0.07	-0.05	-0.06	-0.22	-0.05	-0.15	-0.08	-0.09	0.13	0.13	0.15	0.17
	Splenius Capitis	0.14	0.10	-0.14	-0.13	-0.07	0.05	0.12	0.11	-0.49*	-0.21	-0.14	0.41
	Upper Trapezius	-0.24	-0.14	-0.18	-0.25	-0.64**	-0.56*	-0.30	-0.01	-0.19	0.20	0.29	0.38

SCM= sternocleidomastoid; * P<0.05; ** P<0.01

Figure 1

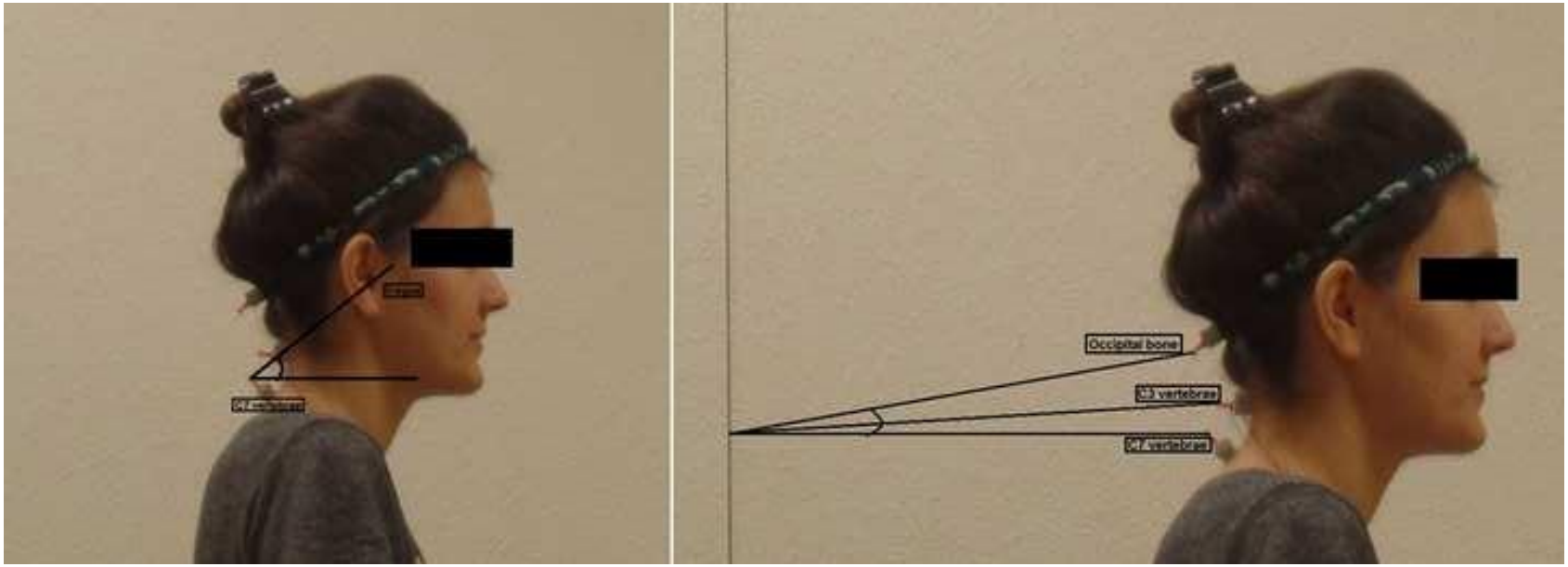


Figure 2

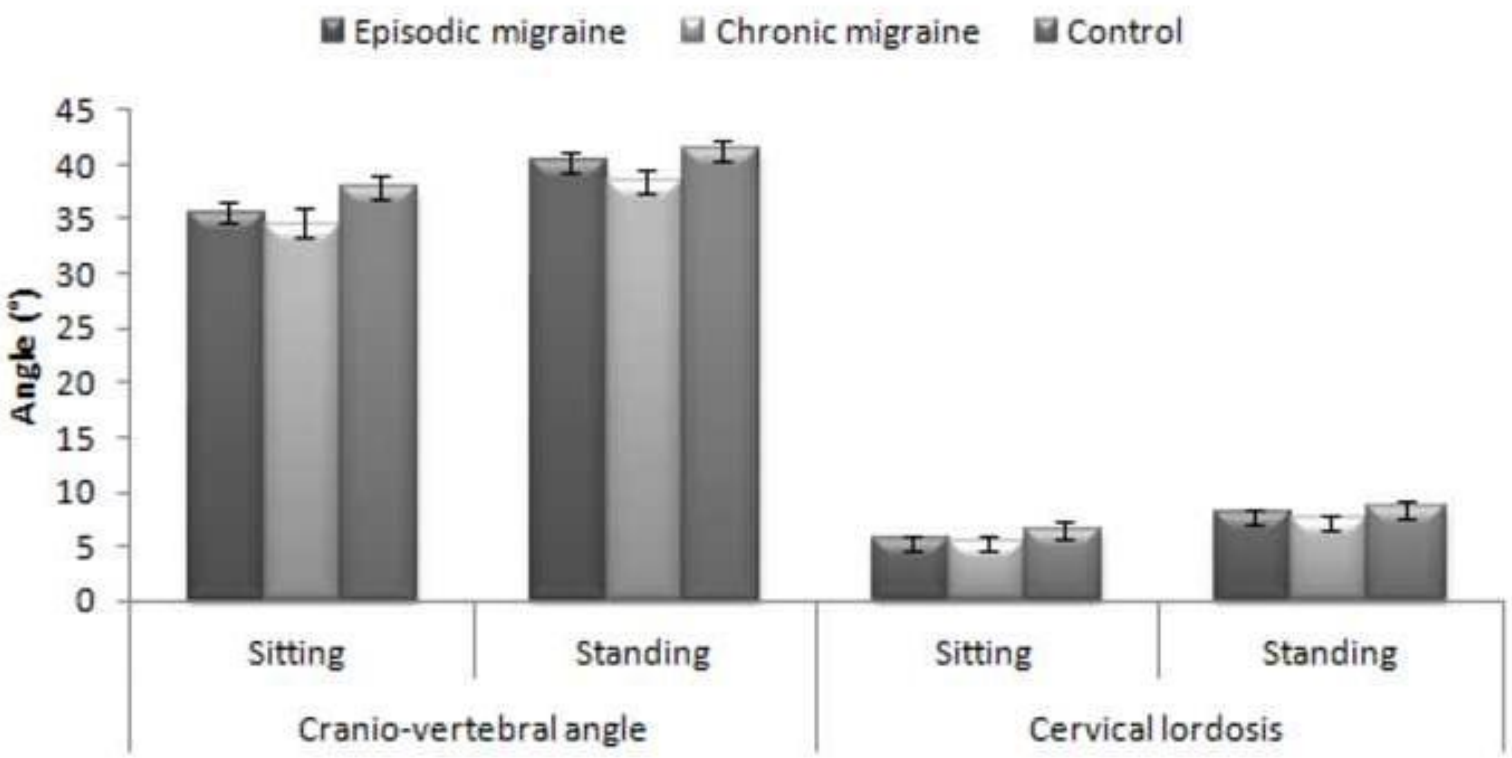
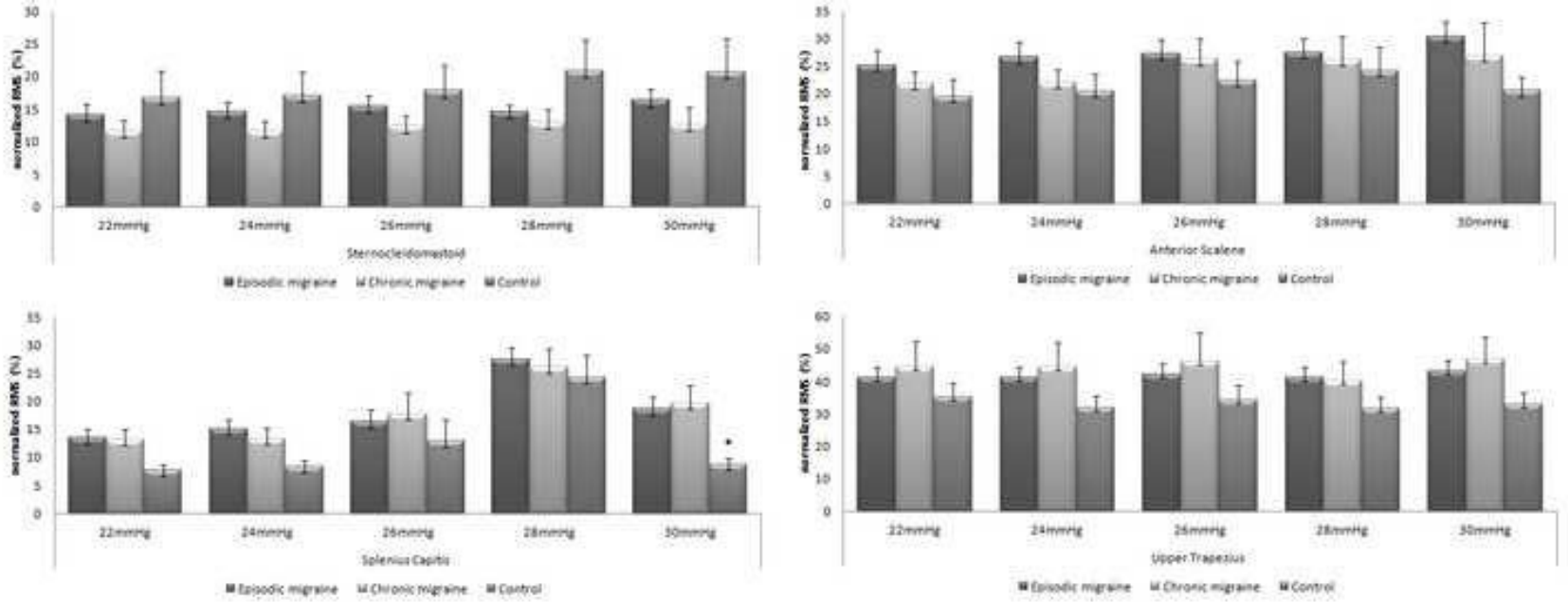

Episodic migraine
Chronic migraine
Control
Angle (°)
45
40
35
30
25
20
15
10
5
0
Sitting
Standing
Sitting
Standing
Cranio-vertebral angle
Cervical lordosis

Figure 3


normalized RMS (%)
22mmHg
24mmHg
26mmHg
28mmHg
30mmHg
Sternocleidomastoid
Episodic migraine
Chronic migraine
Control
Anterior Scalene
Splenius Capitis
Upper Trapezius
*

4 Concluding Remarks

Taking our results together, we can conclude that migraine is associated with a deterioration of neck muscle function and to altered motor control. We can assume an interaction between cervical dysfunction and the chronicity of migraine frequency. Although both groups presented a high prevalence of neck-related disability, subjects with chronic migraine are more likely to report neck-related disability, especially the most disabling forms, than those with episodic migraine. Additionally, the majority of the altered function or motor control could only be evidenced in the chronic form.

Episodic migraine seems to alter the neck muscle response during high-load tasks. Higher rates of myoelectrical discharge and greater fatigability of the upper trapezius were observed during maximal effort in extension. Also, lower amplitude of the agonist and greater activation of the antagonist during MIVC in flexion direction can be observed when contrasted with controls.

Chronic migraine is associated with lower force of neck extension; presenting greater fatigability of the upper trapezius; delay in producing peak force of flexion and lateral bending; and greater antagonist co-activation during MIVC in flexion. Moreover, subjects with chronic migraine presented greater activity of neck extensors during the craniocervical flexion test, indicating a distinct motor control to maintain the stability of the cervical spine.

Finally, it seems that neck muscle activity during low-load craniocervical flexion can be influenced by the presence of active trigger points and extended head posture in subjects with migraine.

Thus, altered muscle function and activity of neck muscles is associated with migraine and neck extensor muscles should receive special attention. These alterations should be considered in the clinical management of migraine and might be helpful in preventing migraine chronification and to reduce overall disability.

However, we must also admit at this point that there is still a very long way to go. Future studies are encouraged to complement the available knowledge regarding neck muscle function and activity in subjects with migraine. Investigations of endurance ability, activities performed in the seated position, and/or assessment under controlled submaximal tasks may more accurately reflect the daily neck muscle demand.

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Attachments

Ribeirão Preto, 04 de janeiro de 2011

Ofício nº 27/2011
CEP/MGV

Prezadas Senhoras,

O trabalho intitulado **"NÍVEL DE INCAPACIDADE DEVIDO À DOR NO PESCOÇO EM INDIVÍDUOS COM CEFALEIAS"** foi analisado "AD REFERENDUM" pelo Comitê de Ética em Pesquisa e enquadrado na categoria: **APROVADO, bem como o Termo de Consentimento Livre e Esclarecido,** de acordo com o Processo HCRP nº 14100/2010.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 196/96 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

DRª MARCIA GUIMARÃES VILLANOVA
Vice-Coordenadora do Comitê de Ética em Pesquisa do HCRP e da FMRP-USP

Ilustríssimas Senhoras
PROFª DRª DÉBORA BEVILAQUA GROSSI
ELISANGELA CRISTINA BIZOLI CASIMIRO(Aluna)
Depto. de Biomecânica, Medicina e Reabilitação do Aparelho Locomotor

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HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
DE RIBEIRÃO PRETO DA UNIVERSIDADE DE SÃO PAULO

FMRP-USP

Ribeirão Preto, 20 de fevereiro de 2013

Ofício nº 509/2013
CEP/MGV

Prezadas Senhoras,

O trabalho intitulado **"AVALIAÇÃO DA FORÇA MÁXIMA E DO CONTROLE MOTOR DA COLUNA CERVICAL PELA DINANOMETRIA E PELA ELETROMIOGRAFIA DE SUPERFÍCIE EM MULHERES COM MIGRÂNEA E MIGRÂNEA CRÔNICA: ESTUDO CONTROLADO",** foi analisado pelo Comitê de Ética em Pesquisa, em sua 360ª Reunião Ordinária realizada em 18/02/2013, e enquadrado na categoria: **APROVADO,** bem como o **Termo de Consentimento Livre e Esclarecido - 21/01/2013,** de acordo com o Processo HCRP nº 16692/2012.

De acordo com Carta Circular nº 003/2011/CONEP/CNS, datada de 21/03/2011, o sujeito de pesquisa ou seu representante, quando for o caso, deverá rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última do referido Termo; o pesquisador responsável deverá da mesma forma, rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última página do referido Termo.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 196/96 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

DRª. MARCIA GUIMARÃES VILLANOVA
Coordenadora do Comitê de Ética em Pesquisa do HCRP e da FMRP-USP

Ilustríssimas Senhoras
LIDIANE LIMA FLORENCIO
PROFª. DRª. DÉBORA BEVILAQUA GROSSI (Orientadora)
Depto. de Biomecânica, Medicina e Reabilitação do Aparelho Locomotor

Hospital Universitario Fundación Jiménez Díaz | idcsalud

Comité Ético de Investigación Clínica

INFORME DEL COMITE ÉTICO DE INVESTIGACION CLINICA

Dra. Olga Sánchez Pernaute, Secretaria Suplente del COMITE ÉTICO DE INVESTIGACION CLINICA DE LA FUNDACION JIMENEZ DIAZ

CERTIFICA:

Que el CEIC-FJD ha evaluado el estudio referido a continuación en la reunión del 10 de junio de 2014 (Acta nº 07/14) y, una vez aceptadas las respuestas a las aclaraciones solicitadas, ha decidido:

A P R O B A R

La propuesta del Promotor para que se realice el Estudio Observacional titulado: **"Evaluación longitudinal de los desórdenes músculo-esqueléticos y su papel desencadenante en pacientes con cefalea de origen tensional",** el cual está previsto que sea dirigido por la **Dr. Carlos Ordás Banderas**, en el Servicio de **Neurología** del Hospital **Rey Juan Carlos** y el **Hospital Infanta Elena de Madrid.**

Además, hace constar que:

1. En dicha reunión se cumplieron los requisitos establecidos en la legislación vigente –Real decreto 223/2004 y Decreto 39/94 de la CAM– para que la decisión del citado CEIC sea válida.
2. El Estudio reúne las normas éticas estándar de nuestra Institución para la realización de este tipo de estudios.
3. Que se cumplen los preceptos éticos formulados en la Orden SAS 3470/2009 y la Declaración de Helsinki de la Asociación Médica mundial sobre principios éticos para las investigaciones médicas en seres humanos y en sus posteriores revisiones, así como aquellos exigidos por la normativa aplicable en función de las características del estudio.
4. El CEIC-FJD, tanto en su composición, como en los PNT cumple con las normas BPC.
5. La composición actual del CEIC-FJD es la siguiente:
   - Dra. Belen Acevedo Marín. *Médico Asistencial*
   - Dra. Mª José Almodóvar Carretón. Farmacéutica de Atención Primaria
   - Dr. Javier Bécares Martínez. ***(Secretario)***. *Farmacéutico de la FJD*
   - Dra. Miriam Blanco Rodríguez. *Médico Asistencial*
   - Dra. Macarena Bonilla Porras. ***(Vicepresidenta).*** *Farmacéutico de la FJD*
   - Dr. Emilio Calvo Crespo. **(Presidente)** *Médico Asistencial.*
   - Dra. Isabel Egocheaga Cabello. *Médico de Atención Primaria*
   - Dr. Ricardo Fernández Roblas. *Médico Asistencial*
   - Dr. Yann Izarzugaza Peron. *Médico Asistencial*
   - Dr. Alberto Lendinez Fornis. *Médico Asistencial*
   - Dra. Isabel Lorda García. *Médico Asistencial*
   - Dra. Dolores Martínez Pérez. *Médico Asistencial*
   - D. Manuel Matamoros Fernández. *Lego no vinculado a la Institución*
   - Dra. Maria Rosario Noguero Meseguer. *Médico Asistencial*
   - Dr. Germán Peces Barba Romero. *Médico Asistencial, Miembro Comité de Investigación*
   - D. Luis Ortega Alba. *Abogado*
   - Dr. Mauro Javier Oruezabal Moreno. *Médico Asistencial*
   - Dr. Francisco Javier Ruiz Hornillos. *Médico Asistencial y Miembro Comité Ética Asistencial.*
   - Dra. Olga Sánchez Pernaute ***(Secretaria Suplente).*** Médico Asistencial
   - Dra. Aranzazu Sancho López. *Farmacóloga Clínico*
   - Dña. Pilar Soriano de la Fuente. *Lego no vinculado a la Institución*
   - Dña. Esperanza Vélez Vélez. DUE
6. Asimismo, hacemos constar que no existe contraprestación económica para el centro ni los investigadores.

Lo que firmo en Madrid a 19 de agosto de 2014

Dra. Olga Sánchez Pernaute
Secretaria Suplente CEIC-FJD

Conocido y conforme:

Verónica García Martínez
Area Gestión Investigación

Vº Bº

Juan Antonio Alvaro de la Parra
Gerente FJD

EO 50/2014_FJD

Universidad Rey Juan Carlos

Rectorado

D. José Luis del Barrio Fernández, Secretario del Comité de Ética de la Investigación de la Universidad Rey Juan Carlos,

CERTIFICA

Que este Comité ha evaluado el proyecto de investigación titulado:

EVALUACIÓN DE LOS DESÓRDENES MÚSCULO-ESQUELÉTICOS COMO NUEVA TÉCNICA PARA SCREENING, DIAGNÓSTICO Y CLASIFICACIÓN DE PACIENTES CON CEFALEA DE ORIGEN TENSIONAL Y MIGRAÑA.

Con número de Registro interno: 23 / 2014

y considera que:

- Se cumplen los requisitos éticos necesarios del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para los participantes.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

Por lo que ha decidido emitir un dictamen **FAVORABLE** para la realización de dicho proyecto, cuyo investigador principal es **Don CÉSAR FERNÁNDEZ DE LAS PEÑAS** de la Facultad de Ciencias de la Salud de la URJC

Lo que firmo en Móstoles a 14 de julio de 2014

Firmado: D. José Luis del Barrio Fernández

Tulipán, s/n E 28933 Móstoles Madrid España Tel. 34 91 665 50 60 Fax 34 91 614 71 20

Hospital Universitario Fundación Alcorcón
SaludMadrid

Comunidad de Madrid

MODELO DE EVALUACIÓN ÉTICA. INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Dña. Ana Tato Ribera, Secretaria del Comité Etico de Investigación Clínica del Hospital Universitario Fundación Alcorcón,

C E R T I F I C A

Que este Comité ha evaluado la propuesta para que se realice el estudio titulado **"Evaluación de los desórdenes musculo-esqueléticos como nueva técnica para screening, diagnóstico y clasificación de pacientes con cefalea de origen tensional y migraña",** considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.

El Investigador se compromete a responder a los informes de seguimiento que desde el CEIC se les requiera

Y que este Comité acepta que dicho registro sea realizado en el Hospital Universitario Fundación Alcorcón por **D. Cesar Fernández de las Peñas (URJC) y por el Dr. Juan Antonio Pareja Grande** como investigadores principales.

Lo que firmo en Alcorcón, a 22 de diciembre de 2014.

Comité Ético de Investigación Clínica

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