Does Mobilization of the Upper Cervical Spine Affect Pain Sensitivity and Autonomic Nervous System Function in Patients With Cervico-craniofacial Pain? A Randomized-controlled Trial

Roy La Touche, PT, MSc,*†‡ Alba Paris-Alemany, PT, MSc,‡
Jeffrey S. Manheimer, PT, PhD, CCTT,§ Santiago Angulo-Díaz-Parreno, MSc,†‡∥
Mark D. Bishop, PT, PhD,‡‡ Antonio Lopéz-Valverde-Centeno, MD, PhD,**
Harry von Piekartz, PT, PhD,†† and Josue Fernández-Carnero, PT, PhD†‡‡

Objectives: The aims were to investigate the effects of anterior-posterior upper cervical mobilization (APUCM) on pain modulation in craniofacial and cervical regions and its influence on the sympathetic nervous system.

Methods: Thirty-two patients with cervico-craniofacial pain of myofascial origin were randomly allocated into experimental or placebo groups. Each patient received 3 treatments. Outcome measures included bilateral pressure pain thresholds assessed at craniofacial and cervical points preintervention, after the second intervention and after the final treatment. Pain intensity and sympathetic nervous system variables (skin conductance, breathing rate, heart rate, and skin temperature) were assessed before and immediately after each intervention.

Results: The pressure pain thresholds in the craniofacial and cervical regions significantly increased (P < 0.001) and pain intensity significantly decreased (P < 0.001) in the treatment group compared with placebo. APUCM also produced a sympathoexcitatory response demonstrated by a significant increase in skin conductance, breathing rate, and heart rate (P < 0.001), but not in skin temperature (P = 0.071), after application of the technique compared with placebo.

Discussion: This study provided preliminary evidence of a short-term hypoalgesic effect of APUCM on craniofacial and cervical regions of patients with cervico-craniofacial pain of myofascial origin, suggesting that APUCM may cause an immediate nociceptive modulation in the trigeminocervical complex. We also observed a sympathoexcitatory response, which could be related to the hypoalgesic effect induced by the technique, but this aspect should be confirmed in future studies.

Key Words: manual therapy, neck pain, temporomandibular disorders, orofacial pain, craniofacial pain

Discomfort resulting from temporomandibular disorders (TMDs) is representative of many chronic craniofacial pain (CCFP) conditions.1 TMD demographics usually consist of working women in the 3rd decade of life with high stress levels.2 TMDs are characterized by a focal site of tenderness that provokes nociceptive input and, when chronic, contributes to the development of central sensitization. Patients with TMDs are known to have greater temporal summation of pain, suggesting hyperexcitability of the central nociceptive system.3,4 More specifically, chronic muscular TMD pain is associated with a general dysfunction of the central nociceptive system that is comitant with central nociceptive neuronal hyperexcitability and dysfunction of the descending inhibitory pain systems.5 Women have a 3 times greater risk of experiencing chronic mastiatory myofascial pain than men.6 Patients with TMDs of myofascial origin are also characterized by a general hypersensibility to mechanical pain stimuli, presenting lower craniofacial pressure pain thresholds (PPT) of both the painful and nonpainful side compared with healthy controls.7

Some studies suggest a functional relationship between the jaw and head-neck with regard to craniofacial and cervical spine and a concomitance between craniofacial pain and neck pain.2,8–10 Patients with craniofacial pain are at twice the risk of experiencing neck pain than the general population.2 Restricted segmental movements of the upper cervical vertebrae (C0-C3) with a greater percentage of upper trapezius and sternocleidomastoid tendon points exist in patients with TMDs compared with a control group.11 In addition, Eriksson et al12 demonstrated coordinated articular patterns of movement between the temporomandibular, atlanto-occipital, and cervical joints, joints that also have known sensory-motor interaction via the trigeminocervical complex (TCC). Disturbance of this connection between jaw and head-neck movements has been identified in patients with whiplash-associated disorders.12

Spinal manual therapy (SMT) is used by physical therapists (PTs) to treat chronic musculoskeletal pain.13

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From the *Department of Physical Therapy, La Salle University Center, Faculty of Health Science, Av. Catedrático Alfonso García Abarca, 7, 28013, Madrid, Spain; †Research Group of Musculoskeletal Pain and Motor Control, Universidad Europea de Madrid, Villaviciosa de Odón; ‡Institute of Neuroscience and Craniofacial Pain (INDCRAN); ††Faculty of Experimental Science, Universidad San Pablo CEU; †‡Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid; †§Department of Surgery, Faculty of Medicine and Dentistry, Universidad de Salamanca, Salamanca, Spain; §§Program in Physical Therapy, Columbia University, NY; ¶Department of Physical Therapy; ¶¶Center for Pain Research and Behavioral Health, University of Florida, Gainesville, FL; and ‡‡Faculty of Business, Management and Social Science, University of Applied Science, Osnabrück, Germany.

The authors declare no conflict of interest.

Reprints: Roy La Touche, PT, MSc, INDCRAN, C/Caños del Peral 11, Bajo Izquierdo, 28013 Madrid, Spain (e-mail: roylatouche@yahoo.es).

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Various techniques such as passive manipulation and mobilization, active mobilization, neuromuscular facilitation, and articular glides are included under the general term of SMT.14–17 Many SMTs have demonstrated hypoalgesic effects. This hypoalgesic effect is not antagonized by naloxone and does not exhibit tolerance,18 supporting the theory that SMTs activate a nonopioid inhibitory system. In addition, a concomitant activation of the sympathetic nervous system (SNS) occurs after SMT, with the degree of activation depending on the technique.19,20

Many studies have investigated the effects of SMT on lower cervical pain,14–16,21 but there is no randomized-controlled trial in which SMT is used to diminish craniofacial pain. George et al22 compared cervical manipulation with a soft tissue technique at the cervical-cranial junction to improve mouth opening in healthy controls, but no significant results were obtained. Another study examined a manual therapy and therapeutic exercise protocol applied at the cervical spine, to treat craniofacial pain of myofascial origin in a cohort intervention study, which resulted in an increase in the PPT in the masticatory muscles and increased mouth opening.23

Consequently, the aims of this study were to extend previous work by investigating the neurophysiological effects of SMT in patients with CCFP of myofascial origin. Specifically, we studied passive anterior-posterior upper cervical mobilization (APUCM). We expected pain sensitivity in the craniofacial and cervical regions to decrease in response to treatment. In addition, we expected to observe the sympathetic influence of this technique on skin conductance (SC), breathing rate (BR), heart rate (HR), and skin temperature (ST).

MATERIALS AND METHODS

Selection and Description of Participants

Thirty-two patients with CCFP of myofascial origin referred from 2 private dental clinics and 3 universities in Madrid, Spain, were recruited from January 2009 to May 2010. We defined the term CCFP of myofascial origin as pain and dysfunction located at the cervical and masticatory muscles. Patients were selected if they met all of the following criteria: (1) a primary diagnosis of myofascial pain as defined by axis I, category Ia and Ib (eg, myofascial pain with or without limited opening of the mouth) of the Research Diagnostic Criteria for Temporomandibular Disorders;24 (2) bilateral pain involving the masseter, temporals, upper trapezius, and suboccipital muscles; (3) a duration of pain of at least 3 months; (4) a pain intensity corresponding to a weekly average of at least 30 mm on a 100-mm visual analog scale (VAS); (5) neck and/or shoulder pain with symptoms provoked by neck postures or neck movement; (6) Neck Disability Index (NDI) ≥ 15 points; and (7) presence of bilateral trigger points (TrPs) in masseter, temporalis, upper trapezius, and suboccipital muscles. TrPs were diagnosed according to the following criteria25: (1) presence of a palpable taut band in the skeletal muscle; (2) presence of a hypersensitive tender spot within the taut band; (3) local twitch response elicited by the snapping palpation of the taut band; and (4) reproduction of referred pain in response to TrP compression.

All patients in the study were examined by a physical therapist with 7 years of experience managing craniofacial and cervical disorders. Patients were excluded if they presented any signs, symptoms, or history of the following diseases: (1) intra-articular temporomandibular disk displacement, osteoarthrosis, or arthritis of the temporomandibular joint, according to categories II and III of the Research Diagnostic Criteria for Temporomandibular Disorders23,28; (2) history of traumatic injuries (eg, contusion, fracture, or whiplash injury); (3) systemic diseases such as fibromyalgia, systemic erythematous lupus, or psoriatic arthritis; (4) neurological disorders (eg, trigeminal neuralgia); (5) concomitant medical diagnosis of any primary headache (tension type or migraine); (6) unilateral neck pain; (7) cervical spine surgery; (8) clinical diagnosis of cervical radiculopathy or myelopathy; and (9) history of previous physical therapy intervention for the cervical region. Each participant received a thorough explanation of the content and purpose of the treatment before signing an informed consent form related to the procedures, which was approved by the local ethics committee in accordance with the Helsinki Declaration.

Research Design

A randomized, double-blind placebo-controlled study was performed. Patients were blind to which intervention they received, and an independent assessor, blind to intervention assignment made the measurements and registered the data. Patients were randomly allocated to either treatment intervention or sham intervention. Randomization was performed by a computer generated random-sequence table created with Graphpad software GraphPad Software Inc., CA) before the beginning of the study. The randomization sequence used a balanced block design in which randomization occurred in blocks of 2.

Sample Size Calculation

A pilot study was performed with 5 patients in the treatment group and 5 patients in the sham group to calculate the sample size. We used data indicative of the percent change in the PPT of the 2 assessed points: 1 at the masseter muscle and 1 at the trapezius muscle.

Sample sizes were calculated to obtain a power of 80% to detect changes in the bilateral contrast of the null hypothesis of equal means between the 2 groups, with 5% significance, taking into account the possibility that the SDs of the groups could be different. According to the sample calculations which took into account the fact that the calculation was based on 2 different variables, we obtained 2 possible results: 14 patients in each group or 16 patients in each group. We decided to include 16 patients per group to anticipate the possible loss of patients.

Demographic and Clinical Data

Each of the participants completed a questionnaire to determine if they met the criteria for inclusion or exclusion. This questionnaire included demographic data, screening questions for TMDs from the American Academy of Orofacial Pain,29 a body chart on which patients marked the location of their pain, and several questions about the characteristics of their pain such as “when did it start?,” “what makes your pain worse?,” “what makes it better?,” and “what kind of pain is it?” To meet the criteria to participate in the study, patients had to pass an initial physical examination performed by a single investigator to rule out the presence of nerve root compression.
Instrumentation and Measurements

Self-reported Variables

Patients completed the Beck Depression Inventory (BDI),\(^{30}\) the State-Trait Anxiety Inventory (STAI),\(^{31}\) and the NDI\(^ {25,26}\) to quantify their psychophysical state. The BDI is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression. There is a 4-point scale for each item ranging from 0 to 3. The results of each item, corresponding to a symptom of depression, are summed to yield a single score for the BDI. A total score of 0 to 13 is considered minimal, 14 to 19 mild, 20 to 28 moderate, and 29 to 63 severe depression. The BDI showed good internal consistency (z coefficient 0.86).\(^ {30}\)

The STAI\(^ {31}\) is a 40-item self-report questionnaire designed to assess symptoms of anxiety. It consists of 2 independent scales, a state anxiety scale and a trait anxiety scale, with 20 items each, resulting in a score between 20 and 80. Higher scores indicate greater levels of anxiety. The state and trait scales explore anxiety as a current emotional state and as a personality trait, respectively.

The NDI\(^ {25,26}\), which measures perceived neck disability, consists of 10 items that assess different functional activities and uses a 6-point scale ranging from 0 (no disability) to 5 (complete disability). The overall score (out of 100) is obtained by adding the score for each item and multiplying by 2. A higher score indicates greater pain and disability. The validity, reliability, and responsiveness of the NDI have been demonstrated.\(^ {36}\)

Pain Intensity

The VAS was used to measure pain intensity of the cervico-craniofacial region at rest and before and after each treatment. The VAS is comprised of a 100 mm horizontal line in which the left side represents “no pain” and the right side represents “worst pain.” The patient placed a mark on the line at the point that they felt represented the intensity of their pain at the time. Pain intensity was quantified by the assessor in millimeters. This scale has proven its reliability and validity for measuring pain intensity.\(^ {32}\)

Pressure Pain Threshold

PPT is defined as the minimum amount of pressure needed to provoke a pain sensation.\(^ {33}\) We used a digital algometer (Model FDX 10; Wagner Instruments, Greenwich, CT) comprised of a rubber head (1 cm\(^2\)) attached to a pressure gauge, which measures in kg with thresholds expressed in kg/cm\(^2\). The protocol consisted of 3 measurements with an interval of 30 seconds between each measurement. The average of the 3 measurements was calculated to obtain a single value for each of the measured points in each of the assessments. This algometric method has high reliability (ICC = 0.91, 95% CI, 0.82-0.97) for measuring PPT.\(^ {34}\) PPTs were assessed bilaterally at 2 points in the masseter muscle (M1 and M2), 2 points in temporalis muscle (T1 and T2), suboccipital muscles, C5 zygapophyseal joint, and upper trapezius muscle. The device was applied perpendicular to the skin, and the patients were asked to raise their hand the moment when the pressure started to change to a pain sensation, at which point the assessor stopped applying pressure. This procedure was performed 3 times: before the first treatment session (pretreatment outcome), after the second treatment session, and after the third treatment session (2 posttreatment outcomes).

Anatomic references for the algometric measurements included the following: M1—2.5 cm anterior to the tragus and 1.5 cm inferior to the zygomatic arch; M2—1 cm superior and 2 cm anterior from the angle of the jaw; T1 (anterior fibers of the muscle)—3 cm superior to the zygomatic arch in the middle point between the end of the eye and the anterior part of the helix of the ear; T2 (middle fibers of the muscle)—2.5 cm superior from the helix of the ear; suboccipital muscles—2 cm inferior to the occipital condyles; C5 zygapophyseal joint—2 cm lateral to the spinous process of C6; trapezius muscle—2.5 cm above the superior medial angle of the scapula.

Changes in the SNS

Several characteristics were measured to assess the SNS: SC, HR, BR, and ST. Measurements were taken before and after each of the 3 treatment sessions. The recording device used was I-330-C2 + 6-channel biofeedback system (J&J Engineering Inc., Poulsbo, WA) the MC-6SY sensor was used to measure SC and ST. During the measurements 2 electrodes were placed on the tip of the second and third fingers of the left hand to measure the SC with the temperature sensor attached to the tip of the fourth finger also on the left hand. The MC-5D electrodes used to measure HR were applied longitudinally at the anterior and radial aspect of the wrists and held with bracers. To measure BR, an MC-3MY breathing sensor was placed around the chest like a belt passing over the xiphoid process.

Procedure

The experiment consisted of 3 treatment sessions. Each patient received 3 sessions over 2 weeks, and the entire experiment lasted approximately 8 months.

The evaluator was a PT with extensive experience in taking the experimental measurements. During the first assessment, pretreatment data were obtained; after measuring the PPT and VAS, the sensors were applied, and the patient was instructed to lie down on a couch and relax. The room temperature was controlled at 25°C. After 10 minutes (time determined for the patient to come to a normal baseline), the first record of the sympathetic parameters was registered. The patient was then randomly assigned to 1 of the 2 intervention groups, and the therapeutic technique was applied. Immediately after finishing the technique, SNS variables were measured, and 5 minutes after the technique, VAS results were registered again. In the second and third treatment session, the SNS variables and VAS were measured using the same protocol (pretreatment and posttreatment data), but PPTs were taken only 5 minutes after the end of the treatment (posttreatment data). Therefore, we obtained 3 pretreatment and 3 posttreatment measurements of SNS and VAS parameters and 1 pretreatment and 2 posttreatment measurements (after the second and third sessions) of PPT.

Treatment Technique

APUCM directly influences the 3 upper cervical segments (C0-C3). The patient was placed in a supine position with a neutral position of the cervical spine. The PT held the occipital region of the patient with both hands to stabilize and maintain the position of the upper cervical structures, while applying a posterior directed force on the frontal region of the patient (anterior to posterior force) with the anterior part of the shoulder. The mobilization was applied at a slow rate of 1 oscillation per 2 seconds (0.5 Hz) controlled
with an MA-30 digital metronome (Korg Inc., Japan). This oscillation rate has been used previously with a different manual therapy technique. The total time of mobilization was 6 minutes. Mobilization was applied in 3 intervals of 2 minutes, with 30 seconds of rest in between, resulting in a total of 7 minutes.

**Sham Technique**

To simulate the treatment technique, the PT applied the same grips used with the treatment technique: 2 hands under the occipital bone with the anterior part of 1 shoulder positioned anterior to the frontal bone, with the patient in supine position. However, mobilization was not applied to the cervical spine. The contact with the patient was held for 3 intervals of 2 minutes with 30 seconds of rest in between.

Both techniques (treatment and sham) were applied by the same PT, and each participant received the following explanation about the intervention: “A physical therapist will apply a technique on your neck with one hand placed on the posterior part of your neck and the other one on your forehead. The purpose is to obtain changes in your neck and craniofacial pain.”

**Statistics**

Statistical analysis was performed with SPSS version 15.0. A Kolmogorov-Smirnov test was used to determine whether the sample was consistent with a normal distribution (P > 0.05). Student t test was used to analyze self-reported psychophysical variables (NDI, STAI, and BDI) and pain duration by comparing the preintervention data (presession 1, presession 2, presession 3). The percent of the total of the means in both groups. A 1-way ANOVA was used to analyze the percent change in group (treatment and sham). Time (ANOVA); the factors analyzed were time (pre-post) and group interactions were also analyzed. Post hoc analysis with Bonferroni corrections was performed for specific comparisons between variables.

To determine differences between sessions in VAS and SNS variables, a 2-way ANOVA was used, which analyzed intersession factor and group × intersession interaction (presession 1, presession 2, presession 3). The percent change for the SNS variables and VAS was obtained relative to the percent change between each session and the percent of the total of the means in both groups. A 1-way ANOVA was used to analyze the percent change in group factor and time factor between sessions (% change session 1, % change session 2, % change session 3). The percent change of the total of the means of the 3 sessions in the treatment and placebo groups was analyzed with a Student t test.

A 3 × 3 mixed-model ANOVA was used to determine the PPT variables (M1, M2, T1, T2, suboccipital, C5, trapezius); the factors were group (treatment or sham), time (pre, post 1, and post 2) and side (right and left). Bonferroni corrections were used for post hoc analysis of specific comparisons between variables. Student t test determined the percent change between groups between the first session (pretreatment) and last session (posttreatment 2) outcomes. Throughout all analyses, statistical significance was set at P < 0.05.

**RESULTS**

Thirty-two patients (21 females and 11 males) with CCFP of myofascial origin were included in this study. No patients dropped out during the study, and no adverse events occurred with the APUCM. The t test did not reveal any significant differences between groups with regard to demographic details and clinical data (P > 0.05), as shown in Table 1. A normal distribution was confirmed with the Kolmogorov-Smirnov test (P > 0.05).

**Pain Intensity**

The ANOVA revealed a significant group × time interaction (F = 135.81; P < 0.001), and significant differences for the time factor (F = 261.7; P < 0.001) and group factor (F = 32.59; P = 0.003) regarding the VAS results. Post hoc analysis also revealed significant differences for the treatment group (P < 0.001), but not for the sham group (P = 0.3) for the descriptive data shown in Table 2. A 2-way repeated-measures ANOVA found significant intersession differences (F = 11.86; P < 0.001) and a group × intersession interaction (F = 17.09; P < 0.001), indicating that the change from session to session was larger for 1 group.

Regarding the percentage of change, a 2-way repeated-measures ANOVA revealed significant differences for group factor (F = 94.24; P < 0.001) and time factor (F = 11.3; P < 0.001), represented in Figure 1A. The t test also revealed significant differences between the percent change of the total of the means for the treatment and sham groups (t = −10.03; P < 0.001).

**Pain Sensitivity**

**Craniofacial Region**

Analysis of the PPT within the craniofacial region was performed by a 3 × 3 mixed-model ANOVA, which revealed a significant effect of time factor [M1 (F = 83.65; P < 0.001); M2 (F = 67.44; P < 0.001); T1 (F = 98.05; P < 0.001); T2 (F = 18.81; P < 0.001)], group factor [M1 (F = 12.27; P = 0.001); M2 (F = 18.35; P < 0.001); T1 (F = 16; P < 0.001); T2 (F = 15.85; P < 0.001)] and group × time interaction [M1 (F = 59.65; P < 0.001); M2 (F = 48.45; P < 0.001); T1

| TABLE 1. Descriptive Data of the 2 Intervention Groups: Treatment and Sham Groups |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Treatment (N = 16) | Sham (N = 16)   | Mean Difference | 95% CI for Mean Difference | t    | P      |
| Mean (SD)                       | Mean (SD)        | Mean (SD)       | Mean Difference | t                | P      |
| Age                             | 33.19 (9.49)     | 34.56 (7.84)    | −1.37           | −7.64 to 4.68    | −0.48  | 0.65  |
| NDI                             | 15.69 (3.26)     | 16.75 (3.94)    | −1.06           | −3.67 to 1.54    | −0.83  | 0.41  |
| Pain duration                   | 11.31 (6.74)     | 10.69 (5.79)    | −0.62           | −5.16 to 3.91    | −0.28  | 0.83  |
| BDI                             | 13.63 (3.64)     | 12.38 (4.41)    | 1.25            | −2.67 to 3.17    | −0.17  | 0.86  |
| STAI                            | 25.75 (5.63)     | 24.75 (4.66)    | 1              | −2.73 to 4.73    | −0.54  | 0.58  |

BDI indicates Beck Depression Inventory; CI, confidence interval; NDI, Neck Disability Index; STAI, State-Trait Anxiety Inventory; t, t test value.
TABLE 2. Descriptive Statistics for Sympathetic Nervous System Parameters and Pain Intensity, for Pretreatment and Posttreatment Assessments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment (Mean±SD)</th>
<th>Posttreatment (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>Pre 1: 1.84±0.61</td>
<td>Post 1: 2.10±0.78</td>
</tr>
<tr>
<td></td>
<td>Pre 2: 2.2±0.58</td>
<td>Post 2: 2.21±0.61</td>
</tr>
<tr>
<td></td>
<td>Pre 3: 69.56±6.3</td>
<td>Post 3: 71.25±4.39</td>
</tr>
<tr>
<td></td>
<td>Pre 4: 67.87±7.35</td>
<td>Post 4: 67.31±6.6</td>
</tr>
<tr>
<td>HR</td>
<td>Pre 1: 2.0±0.43</td>
<td>Post 1: 2.34±0.38</td>
</tr>
<tr>
<td></td>
<td>Pre 2: 2.25±0.61</td>
<td>Post 2: 2.27±0.55</td>
</tr>
<tr>
<td></td>
<td>Pre 3: 73.16±5</td>
<td>Post 3: 75.1±2.88</td>
</tr>
<tr>
<td></td>
<td>Pre 4: 63.81±7.56</td>
<td>Post 4: 63.31±6.73</td>
</tr>
<tr>
<td>RR</td>
<td>Pre 1: 15.31±2.76</td>
<td>Post 1: 15.63±1.9</td>
</tr>
<tr>
<td></td>
<td>Pre 2: 16.31±4.13</td>
<td>Post 2: 18.38±3.7</td>
</tr>
<tr>
<td></td>
<td>Pre 3: 14.9±2.99</td>
<td>Post 3: 14.28±2.7</td>
</tr>
<tr>
<td></td>
<td>Pre 4: 28.42±4.39</td>
<td>Post 4: 27.53±5.1</td>
</tr>
<tr>
<td>ST</td>
<td>Pre 1: 31.45±3.45</td>
<td>Post 1: 32.44±3.21</td>
</tr>
<tr>
<td></td>
<td>Pre 2: 32.44±3.21</td>
<td>Post 2: 29.56±3.76</td>
</tr>
<tr>
<td></td>
<td>Pre 3: 29.11±4.07</td>
<td>Post 3: 30.46±3.67</td>
</tr>
<tr>
<td></td>
<td>Pre 4: 28.57±3.61</td>
<td>Post 4: 28.57±3.61</td>
</tr>
<tr>
<td>VAS</td>
<td>Pre 1: 43.88±7.3</td>
<td>Post 1: 31.06±8.83</td>
</tr>
<tr>
<td></td>
<td>Pre 2: 29.66±8.97</td>
<td>Post 2: 18.31±9.18</td>
</tr>
<tr>
<td></td>
<td>Pre 3: 31.06±3.26</td>
<td>Post 3: 29.31±11.8</td>
</tr>
<tr>
<td></td>
<td>Pre 4: 24.31±8.51</td>
<td>Post 4: 42.56±6.88</td>
</tr>
<tr>
<td>BR</td>
<td>Pre 1: 4.32±9.41</td>
<td>Post 1: 45.13±7.9</td>
</tr>
<tr>
<td></td>
<td>Pre 2: 29.66±8.97</td>
<td>Post 2: 42.56±6.88</td>
</tr>
<tr>
<td></td>
<td>Pre 3: 28.57±3.61</td>
<td>Post 3: 42.56±6.88</td>
</tr>
</tbody>
</table>

BR indicates breathing rate; HR, heart rate; SC, skin conductance; ST, skin temperature; VAS, visual analog scale.

F = 83.57; P < 0.001); T2 (F = 16.48; P < 0.001), but not for side factor [M1 (F = 0.94; P = 0.76); M2 (F = 0.13; P = 0.72); T1 (F = 0.009; P = 0.92); T2 (F = 0.64; P = 0.43)]. Post hoc testing revealed significant differences between the 3 sessions for the treatment group (P < 0.001) but not for the sham group (P > 0.05) at all craniofacial points; descriptive data are shown in Table 3.

The t test revealed significant differences in the percent change in PPT at the right and left craniofacial points. Figure 2 shows the percent change in PPT from the pretreatment and final posttreatment assessment.

Cervical Region
A 3 × 3 mixed-model ANOVA revealed a significant time effect of the suboccipital musculature (F = 96.33; P < 0.001), C5 zygopophyseal joint (F = 52.37; P < 0.001), trapezius muscle (F = 57.41; P < 0.001), and a group by time interaction at the suboccipital region (F = 64.12; P < 0.001). However, this was not the case for side factor [suboccipital muscles (F = 1.22; P = 0.27); C5 zygopophyseal joint (F = 1.8; P = 0.18); trapezius muscle (F = 1.57; P = 0.22)]. Post hoc analysis revealed significant differences in the PPT for the 3 sessions of the treatment group (P < 0.001), but not the sham group (P = 0.73). The descriptive data of the SC are shown in Table 2. A 1-way repeated-measures ANOVA found no significant intersession differences (F = 0.001; P = 0.97) or group by intersession interaction (F = 0.32; P = 0.57).

ANOVA revealed significant differences in the percent change between treatment sessions for the group factor (F = 31.02; P < 0.001), but not the time factor (F = 0.72; P = 0.48), as shown in Figure 4A. The t test revealed significant differences between percent change of the total means of treatment and sham groups (t = 6.11; P < 0.001).

Breathing Rate
ANOVA revealed a significant group by time interaction (F = 8.91; P = 0.006) and a main effect of group (F = 4.36; P = 0.045), but not time (F = 0.22; P = 0.63), for changes in BR. Post hoc analysis revealed significant differences for the treatment group (P = 0.02), but not the sham group (P = 0.08). The descriptive data of the BR are shown in Table 2. A 1-way repeated-measures ANOVA found no significant differences for intercession (F = 0.13; P = 0.87) or for group by intersession interaction (F = 0.29; P = 0.74).

SNS
Skin Conductance
The ANOVA revealed a significant group by time interaction (F = 10.75; P < 0.001), an effect of time (F = 118; P < 0.001), and an effect of group (F = 10.45; P = 0.003) for changes in SC. Post hoc analysis revealed significant differences in the treatment group (P < 0.001), but not the sham group (P = 0.73). The descriptive data of the SC are shown in Table 2. A 1-way repeated-measures ANOVA found no significant intersession differences (F = 0.001; P = 0.97) or group by intersession interaction (F = 0.32; P = 0.57).
TABLE 3. Descriptive Statistics of PPT Assessed Pretreatment, Posttreatment 1 After the Second Session, and Posttreatment 2 After the Third Session, Taken Bilaterally

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Left</th>
<th>Sham</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post 1</td>
<td>Post 2</td>
<td>Pre</td>
<td>Post 1</td>
</tr>
<tr>
<td>Orofacial region</td>
<td>M1</td>
<td>2.13 ± 0.37</td>
<td>3.03 ± 0.5</td>
<td>3.46 ± 0.45</td>
<td>2.12 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>2.12 ± 0.44</td>
<td>2.88 ± 0.44</td>
<td>3.4 ± 0.38</td>
<td>2.18 ± 0.39</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>2.76 ± 0.49</td>
<td>3.52 ± 0.5</td>
<td>4.11 ± 0.55</td>
<td>2.69 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>3.97 ± 0.48</td>
<td>3.59 ± 0.5</td>
<td>3.95 ± 0.58</td>
<td>2.8 ± 0.56</td>
</tr>
<tr>
<td>Cervical region</td>
<td>Suboccipital</td>
<td>2.36 ± 0.34</td>
<td>3.33 ± 0.29</td>
<td>3.95 ± 0.22</td>
<td>2.28 ± 0.35</td>
</tr>
<tr>
<td></td>
<td>C5</td>
<td>2.47 ± 0.42</td>
<td>3.09 ± 0.65</td>
<td>3.63 ± 0.52</td>
<td>2.46 ± 0.45</td>
</tr>
<tr>
<td></td>
<td>Trapezius</td>
<td>2.61 ± 0.38</td>
<td>3.51 ± 0.42</td>
<td>4.13 ± 0.67</td>
<td>2.66 ± 0.37</td>
</tr>
</tbody>
</table>

Mean ± SD.

PPT indicates pressure pain thresholds.

A 1-way ANOVA revealed significant differences in percent change of BR for the group factor (F = 11.34; P = 0.002) but not for time (F = 1.03; P = 0.36) as shown in Figure 4B. The t test revealed significant differences between the percent change of the total of the means for the treatment and sham groups (t = 3.07; P = 0.004).

Heart Rate

ANOVA revealed a significant group × time interaction (F = 54.14; P < 0.001) and a main effect of group (F = 19.4; P < 0.001), but not time (F = 0.14; P = 0.71), for changes in HR. Post hoc analysis revealed significant differences in the treatment group (P < 0.001) and the sham group (P < 0.001); HR data are shown in Table 2. A 1-way repeated-measures ANOVA found no significant intersession differences (F = 1.5; P = 0.23) or group × intersession interaction (F = 0.45; P = 0.63).

Regarding the percent change in HR, a 1-way repeated-measures ANOVA revealed significant differences for group factor (F = 53.66; P < 0.001), but not time factor (F = 1.02; P = 0.36), as shown in Figure 4C. Significant differences between the percent change of the total of the means for the treatment and sham groups (t = 7.37; P < 0.001) were observed.

Skin Temperature

The ANOVA did not reveal any significant group × time interaction (F = 3.49; P = 0.071), time factor effect (F = 1.62; P = 0.2), or group factor effect (F = 0.53; P = 0.46) for changes in ST. The descriptive data of the ST are shown in Table 2. A 1-way repeated-measures ANOVA found no significant intersession differences (F = 2.84; P = 0.06) or group × intersession interaction (F = 0.25; P = 0.77).

Regarding percent change in ST, a 1-way repeated-measures ANOVA did not reveal a significant difference in group factor (F = 3.25; P = 0.08) or time factor (F = 2.74; P = 0.07), as shown in Figure 4D. The t test did not reveal a significant difference in the percent change of the...
DISCUSSION

Our findings demonstrate that the APUCM technique applied at a rate of 0.5 Hz significantly increased SNS activity and produced short-term hypoalgesic effects. We are not aware of any previous studies that have measured hypoalgesic effects in the cervical and craniofacial regions using APUCM. We therefore contend that this is the first time that this specific manual mobilization technique applied at the aforementioned frequency has been investigated, and our data indicate significant differences between the experimental and control groups.

An increase in PPT was observed after the second intervention compared with the presession data and after the third intervention compared with the first posttreatment assessment, which is indicative of a maintained increase over the successive sessions. With regard to pain intensity, it is important to note the decrease in the VAS after each session, which was maintained from one session to the next and indicates a 41.7% decrease in pain intensity from the 3 applications. A change in the SNS, as evidenced by changes in SC, BR, and HR, was noted after each session, but this trend reversed and was not maintained from one session to the next. Upon comparing the first, second, and third pretreatment outcomes, it was apparent that the SNS values returned to a normal state of SNS activity. We suggest that the effect produced by the technique could be due to the influence of transient sympathoexcitation on pain mechanisms. Our contention is that the physiological effects produced by the APUCM technique influence the suboccipital posterior sympathetic network and TCC and act to inhibit or gate myofascial pain within the cervico-craniofacial region.

Clinical Effectiveness

The results of clinical pain intensity measured by the VAS indicate a decrease in the patients’ experience of pain at rest with significant differences between treatment and sham groups. Patients who received the intervention reported a decrease of 29.13 mm in VAS between the pretreatment and third posttreatment assessment. Todd et al. have stated that a minimal clinically significant change in VAS may be at least 13 mm, whereas more recently, Bird and Dickson have contended that a clinically significant VAS change depends on the baseline VAS of the participant and that a change of 13 mm would be clinically significant for a baseline VAS < 34 mm, a change of 17 mm for a baseline VAS between 34 and 67 mm, and a change of 28 mm for a baseline VAS > 67 mm. The more specific guidelines of Bird and Dickson are supported by Emshoff and colleagues in a study of chronic TMD pain patients.

FIGURE 4. Percent change between the 3 sessions (mean of preintervention and postintervention) for treatment and sham groups. A, skin conductance; B, heart rate; C, breathing rate; D, skin temperature.
They established that to be clinically significant, patients with a higher pain baseline must demonstrate a greater VAS reduction than those with a lower baseline, and the minimal change should be of $−19.5\,\text{mm}$ or $−37.9\%$ of the VAS.\textsuperscript{37} Our findings are clinically significant according to the guidelines of Todd et al, Bird and Dickson, or Emshoff et al.\textsuperscript{35–37}

**SNS Response**

Previous studies have noted similar effects in the variables that we measured after SMT in the cervical region.\textsuperscript{15,17,19,20,38} We observed an increase of $83.75\%$ in SC, which is similar to that observed by Chiu and Wright\textsuperscript{19} and Sterling et al\textsuperscript{15} who observed increases of approximately $50\%$ to $60\%$ and $16\%$, respectively. Studies in which SMT was applied to other body locations also noted similar changes in SC. A $16.85\%$ increase in SC was observed after a thoracic mobilization applied to T4,\textsuperscript{39} and a $13.5\%$ increase in SC was observed after lumbar mobilization.\textsuperscript{40}

A similar effect was noted for HR. We observed an increase of $6.06\%$ compared with previous studies that reported changes of $10.5\%$,\textsuperscript{38} $13\%$,\textsuperscript{20} and $4.5\%$.\textsuperscript{17} A significant change in HR in the sham group was also noted. HR decreased by $−5.5\%$ in the sham group, which could indicate that the treatment can increase HR, whereas the sham application is similar to a touch massage technique that results in a decrease of SNS activity.\textsuperscript{41}

Previous studies of BR have reported increases of $44\%$,\textsuperscript{38} and $36\%$.\textsuperscript{20} In our study, we observed a $10.4\%$ increase in BR in the experimental group. This discrepancy could be due to the type of mobilization that we applied. Previous studies that used lateral cervical glides or posterior-anterior mobilization techniques at a frequency of $2\,\text{Hz}$. A significant change was not obtained in ST despite a downward trend in both treatment and sham groups, as noted by Chiu and Wright.\textsuperscript{19} However, a significant decrease of $2.5\%$ in ST was obtained in another study.\textsuperscript{15}

The results of Sterling et al\textsuperscript{15} correlate with our data with respect to the tendency of ST to decrease and the noted change in SC. Furthermore, significant changes in blood pressure, which we did not record, have been observed by Paungmali et al.\textsuperscript{17} Vicenzino et al.\textsuperscript{20} and McGuiness et al.\textsuperscript{38} These results confirm that gentle manual mobilization techniques on the cervical spine can confer positive physiological effects.

**Hypoalgesic Effects**

Our data indicate that the APUCM technique produces hypoalgesic effects, as demonstrated by PTT measurements made by an algometer, and support a significant difference between the treatment and sham groups. Sterling et al\textsuperscript{15} demonstrated that a unilateral posterior-anterior mobilization applied on the side of pain increased the PPT by $23\%$ on the side of treatment in patients with chronic idiopathic neck pain. We observed increases in PPT between $64\%$ and $77\%$ for the masseter muscle points, between $38\%$ and $59\%$ at temporal muscle points and between $47\%$ and $79\%$ for the cervical points after 3 treatments of APUCM. The greater change in PPT observed in our study and others may be because our study investigated short-term outcomes (3 treatment sessions) instead of intermediate outcomes (1 treatment session), due to the applied technique and the frequency of mobilization and is indicative of a real bilateral hypoalgesic effect at both regions.

Previous research has investigated the effect of spinal mobilization on cervical and lumbar regions and reported positive results.\textsuperscript{15,20,40,42} Sterling et al\textsuperscript{15} noted a difference between the improved PPT in the painful side and the nonpainful side, indicating a unilateral effect from a unilateral technique. Our study demonstrates a bilateral increase in PPT in both cervical and craniofacial regions. This difference could be due to the central application of the technique in this study as opposed to the unilateral application of Sterling et al.

**Manual Therapeutic Neurophysiology**

Research in SMT has focused on the neurophysiological effects of manual manipulation and mobilizations with data suggesting activation of descending pain inhibitory systems upon short-term (initial) hypoalgesic effects.\textsuperscript{43–45} Skyba et al\textsuperscript{46} showed that mobilization of the hyperalgesic knee joint in rats produced an antihyperalgesic effect. This effect, which maintained after spinal blockage of opioid or noradrenergic inhibitory mechanisms via corticospinal projections from the periaqueductal gray matter (PAG).\textsuperscript{47} Implications relate to noradrenaline, a PGA neurotransmitter that is more effective at inhibiting mechanical nociception than thermal nociception, which seems to be serotoninergically mediated.\textsuperscript{47,48} Others have demonstrated that SMT might be the ideal stimulus for PAG mediated nonopiod analgesia, hypalgesia, sympathoexcitatory effects, and changes in motor activity.\textsuperscript{15,17,20,49} In the present study, we obtained both a sympathoexcitatory and hypoalgesic effect after the APUCM technique, which supports the fact that the d-PAG is influenced by the SMT technique.

One controversial issue surrounding manual therapy is whether a localized segmental and/or extrasegmental effect is produced by SMT. Previous research has shown that SMT improves symptoms distal to the segment where it is applied; that is, manipulation applied at the thoracic spine after cervical or thoracic SMT,\textsuperscript{15,39} and in the lower extremities after lumbar mobilization.\textsuperscript{40} It is clear that SMT activates central structures that concurrently activate sympathoexcitatory and hypoalgesic effects as demonstrated in our research and in that of others.\textsuperscript{15,20} The presence of an extrasegmental effect may indicate activation of the d-PAG and could be mediated by various descending pain inhibitory pathways and associated tracts of the TCC that allow for afferent and efferent transmission between the cervical and craniofacial regions.\textsuperscript{15,42}

**Nociceptive Modulation and the TCC**

The increase in PPT caused by the APUCM technique on the craniofacial region provides additional clinical sup-
port for pain modulatory mechanisms in the TCC. A review performed in 1998 outlined neurophysiological coupling between craniofacial and cervical systems.\textsuperscript{35} It has been observed that manual therapeutic applications to the cervical region provoked a pain reducing effect in the head and face. Mellick and Mellick\textsuperscript{54} and Mellick et al\textsuperscript{55} observed that applying a bilateral intramuscular injection of small amounts of 0.5% bupivacaine at the cervical region caused a decrease in facial pain and headaches. In addition, Carlson et al\textsuperscript{56} demonstrated that an infiltration of 2% lidocaine on an active TrP of the trapezius muscle significantly reduced pain and electromyographical activity of the ipsilateral masseter.

The only previous study of manual interventions to the cervical spine to manage craniofacial pain was performed by La Touche et al. This study reported similar results to our study: improved PPT at the masseter and temporalis muscles after a manual therapy protocol directed to the cervical spine combined with a deep neck flexors training program.\textsuperscript{23}

Convergence pathways between cervical and trigeminal sensory afferents in the TCC are fully supported.\textsuperscript{52,57,58} Stimulation of an upper cervical root, such as manipulation of the greater occipital nerve, has produced changes in the TCC neurons. This supports the concept that perception of cranial pain is due to a functional convergence between trigeminal and cervical fibers in the TCC\textsuperscript{59,60} and provides a potential rationale for the relationship between headaches and arm and trunk pain.\textsuperscript{51}

Direct stimulation of the greater occipital nerve (cervical input) increases metabolic activity of the TCC\textsuperscript{62} and trigeminal nociceptors release neuropeptides, such as substance P, from laminae I and II that diffuse to laminae III to V depending on the intensity of the stimulus.\textsuperscript{63} The TCC itself is formed by the upper cervical dorsal horns and the trigeminal nucleus caudalis, which allows nociceptive input to be transmitted from the TCC to higher centers.\textsuperscript{84} Pain modulatory structures such as the PAG, dorsolateral pontomesencephalic tegmentum, and rostral ventromedial medulla control the TCC-mediated generation of antinoceptive or pronociceptive states.\textsuperscript{57,58,65}

In summary, we propose a neurobiomechanical hypothesis to explain the possible mechanism by which a manual therapeutic technique causes a hypolgesic effect in craniofacial and cervical regions. This technique primarily influences the upper cervical region (C1-C3), which is anatomically related to the occipital bone. We believe that an anterior-posterior glide of the upper cervical structures provokes an improved arthokinematic relationship of the target region thereby generating improved pain-free range of movement and concomitant suboccipital muscle relaxation. A secondary effect might reduce mechanical forces on the upper cervical neurovascular structures, thereby interrupting or inhibiting input and reducing TCC sensitization by activating descending pain inhibitory systems.

In addition, the TCC is the main nucleus that receives nociceptive information from the face, head, and neck.\textsuperscript{86} Neurons inside the nuclei are considered multimodal neurons and can receive 2 or more inputs from different origins, such as cervical nerve roots, when manual therapy is being applied. The input generated from the cervical region can alter the nociceptive processing in the TCC and, as a result, produce a hypolgesic effect at the facial region. Finally, another possible mechanism to explain the effect of our manual intervention is that descending pain inhibitory systems can be activated by SMT on the cervical spine by spinal noradrenergic and serotoninergic pathways from the dorsolateral pons and rostral ventral medulla.\textsuperscript{52,66}

**Study Limitations**

Although the results of our research are positive, we only measured short-term changes without follow-up testing. We only measured SC and ST on the right side. Other studies investigating sympathetic activation after SMT treatment only measured one side of the body, usually the treated side. Perry and colleagues applied a unilateral lumbar mobilization and measured sympathetic activity at both lower extremities. They only observed significant activation in the treated side but did observe a tendency toward sympathetic activation in the untreated side.\textsuperscript{60} It would have been interesting to observe if central mobilization activates SNS with the same intensity in both upper extremities and if it has any effect on lower extremities. It also could have been interesting to measure SC and ST directly on the facial region. We did not measure distal PPT; therefore, due to a lack of information, we cannot provide a complete discussion about the general or segmental effect of the APUCM technique.

This is the first time this type of mobilization at a frequency of 0.5 Hz has been used in a clinical randomized-controlled trial. Because different techniques require different frequencies of application to provoke stronger changes, it would be of interest to test the same mobilization at different frequencies of application.

**Clinical Implications**

We have demonstrated that craniofacial pain can be modulated through an upper cervical treatment (mobilization). The presence of craniofacial pain is a predictor factor for neck pain.\textsuperscript{9,67} It is interesting to treat this type of patient with a technique that has proven effects at the craniofacial segment that can also treat a possible neck dysfunction. This technique might be contraindicated in patients with cranioocular hyperperfusion syndrome due to the movement the APUCM provokes at the upper cervical spine and the risk this entails.\textsuperscript{68}

Chronic pain can be maintained by SNS modulation through the peripheric adrenorreceptor excitation of catecholamine.\textsuperscript{69} Chronic TMD patients seem to present a dysregulation of β-adrenergic activity, which contributes to altered cardiovascular and catecholamine responses.\textsuperscript{70} The dysregulation of SNS can contribute to the severity and maintenance of pain. The influence of APUCM on SNS activity makes this technique an interesting tool to treat patients with CCFP of myofascial origin and patients with facial allodynia, in which other techniques applied directly on the face would be contraindicated.

**CONCLUSIONS**

We demonstrate that APUCM reduces pain intensity and increases PPT in the cervical and craniofacial regions. APUCM also causes sympathoexcitation, which confirms a sympathetic effect. These results indicate an influence of the mobilization on the CNS (medullar or supramedullar effect). This study provides preliminary evidence of the short-term hypolgesic effect on the craniofacial and cervical regions of patients with CCFP of musculoskeletal origin, suggesting that APUCM may cause an immediate nociceptive modulation at the TCC.
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