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Physical therapy treatment for facial and jaw pain associated with trigeminal neuralgia using Systemic Manual Therapy (SMT)

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ABSTRACT

Objective: This study aimed to evaluate the effectiveness of Systemic Manual Therapy using a HOAC-APD model to treat trigeminal neuralgia-associated facial pain (TN).
Design: Cohort retrospective multivariate analysis using a modified adaptive platform design.
Methods: Overall progress across episode of care and average rate of improvement in TN symptoms and overall complaints was measured in 85 patients after using 99 different combinations of Systemic Manual Therapy protocols.
Results: When comparing scores from the beginning and end of the episode of care, 66 % of patients reported improvement in trigeminal neuralgia or facial pain complaints. The average improvement was 1.88/9 ($p < 0.001$) and the overall improvement was 12.01/90 ($p < 0.001$). Thirteen combinations containing eight distinct protocols were found to be better than the average. Five of the protocols effectively addressed central sensitization (UD, Barral, Barral-CVVT, LAUG, VTCP); one protocol was hypothesized to have a direct effect on the trigeminal system (SYMPN), and two protocols could have been effective because of either direct or desensitization effects (CCCV and DCS).
Discussion and conclusion: This study demonstrated that TN can be effectively treated by focusing on central sensitization, which is preserved by the continuous input of several self-reinforcing loops into the LC-NA system. This study supports the hypothesis that central sensitization can be treated by creating intermittent disruption of these self-reinforcing loops.

1. Introduction

Trigeminal neuralgia-associated facial pain (TN), although relatively rare (16–30 per 100,000) [17], is one of the most debilitating and difficult pain conditions to treat. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), there are three classifications of TN: Classic, secondary, and idiopathic [15]. Possible causes or contributing factors include demyelination due to neurovascular compression [14], post-herpetic or other viral or bacterial infections, facial trauma [25,28], and central sensitization [30].

Medical management includes, but is not limited to, medications such as gabapentin [13] and pregabalin [3], surgical decompression [31], trigeminal nerve blocks [19,25], radiofrequency ablation [2] and modalities such as transcutaneous nerve stimulation (TENS) [29], low-level laser therapy, and transcranial electromagnetic stimulation [23]. All of these approaches offer some symptomatic benefits, but most are temporary or can have significant side effects.

The purpose of this study was to explore the efficacy of a previously unreported approach to the treatment using Systemic Manual Therapy (SMT) [5]. By doing so, we hope to help establish a better standard of care that can be replicated or used as a benchmark for comparison with the efficacy of other interventions.

To develop an acceptable standardized treatment, we enlisted two models (HOAC) [20,21] and Adaptive Platform Design (APD) [12].

The HOAC model includes several elements. During the initial patient evaluation, a patient-identified problem list (PIP) and non-patient-identified problem list (NPIP) were generated through interviews and examinations. This process results in several complementary (or competing) hypotheses that include theories for both etiology and the basis for intervention, as well as a treatment plan that includes these interventions. The second part of the HOAC model calls for periodic reassessment of both the existing hypotheses and the effectiveness of treatment, and the continuous synthesis of new hypotheses and interventions.

The APD model was initially introduced during the Ebola outbreak in 2014 [18] to allow for a faster evaluation of new emerging therapies by

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comparing multiple interventions against the existing optimal standard of care (oSOC). Once an intervention is found to be better, it is incorporated into a new oSOC, to which all new interventions are compared.

Conceptually, the second part of the HOAC model and APD are similar. Both models aimed to refine the treatment standard and establish a better standard on a continuing basis. However, the key difference between the two models is that the HOAC is a clinical tool that relies on a single subject (anecdotal observation), whereas the APD model determines the best intervention based on statistical differentiation.

To establish an oSOC for a number of difficult conditions, including TN, we looked for ways to allow us to take the anecdotal practical approach of the second part of the HOAC and convert it into a more rigorous approach employed when using the APD method.

To use the HOAC in a manner similar to the APD model, we identified the need for several essential features that are not part of the current HOAC: a valid PIP-specific outcome measure, a standardized provision of care, and a statistical analysis tool that would control for the obvious internal validity threats associated with measuring repeated multiple interventions in a true clinical setting.

The specific outcome measure used for this study was the Patient Identified Problem (PIP) scale [6]. The PIP scale is a 1–10 (half point permitted) scale. The patient can score between 1 (which denotes that the problem is not currently active) and 10 (which indicates maximal intensity). Problems were examined both individually and as a cumulative score. The cumulative score was calculated according to the following formula: PIP = SUM (individual score/number of problems) $\times$ 10 (adding the scores of all individual problems, dividing the total by the number of individual problems, and then multiplying by 10). Symptoms were graded by the patient whenever possible to decrease the examiner bias. Scoring was always performed at the next visit and not immediately after the treatment. The PIP scale had a specificity and sensitivity of 91.46 % and 64.45 %, respectively, and an ICC score of 0.96. Minimal clinically important change (MCID) for change observed in the whole scale is 3.8 (95 % CI 1.4–8.2), and for an individual problem, score change is 0.89 (95 % CI 0.33–1.5).

Intervention standardization was accomplished using Systemic Manual Therapy (SMT) protocols [5]. These protocols have been developed and standardized over the past few decades by incorporating individual techniques from several osteopathic and physical therapy methods, such as fascial counterstrain (FCS) [26], Barral [1], integrative manual therapy (IMT) [4] and muscle energy techniques (MET) [16].

The Halili Physical Therapy Statistical Analysis Tool (HPTSAT) was used for the analysis while controlling for internal validity threats. The HPTSAT controls for validity threats such as repeated measures and other confounding factors by comparing the average rate of change (ARC5) in outcome scores when an SMT protocol or sequence of protocols is used to when they are not. In the clinical setting, we can use the HPTSAT in a semi-qualitative manner to identify the emerging potential of certain interventions; however, to achieve the level of quantitative differentiation offered in the APD model, we used the stricter established criterion of the HPTSAT to differentiate an intervention from the oSOC. The HPTSAT criterion was established in the following manner: a protocol or protocol combination was determined to be better than the oSOC if it demonstrated a difference from it in the ARC_5 with a p value < 0.05, in each of the following: Welch's t test, Mann-Whitney test (MW), and analysis of variance (ANOVA). In addition, the protocol or protocol combinations also needed to have three other important elements: an $n > 20$, an effect size (Hedges' g) ≥ 0.2 and a PIP score for ARC5 $\geq$ MCID 95 % CI (.33 for individual score and 1.4 for the overall PIP scale).

By adding these three elements, we established a combined approach called the HOAC-APD. This approach was previously used to establish a protocol for treating patients with respiratory issues [7].

Development of hypotheses: As discussed previously, under the HOAC model, for each identified PIP, one or more hypotheses for pathology and effective treatment have been developed. Although each PIP can have a separate approach in the clinical setting, for the purpose of this investigation, we focused on why TN had developed and what interventions should be effective. As these hypotheses were developed, two important factors need to be considered. First, in addition to identifying the initial cause of injury, we must ask why the symptoms do not improve. The second factor to consider is that the intervention is not intended to replace or repair the injured tissue but rather to remove obstacles so that the body can complete its own repair process.

For etiology, we adopted two complementary hypotheses: central sensitization and direct mechanical or circulatory compromise of the trigeminal nerve complex.

2. Central sensitization

To understand the mechanisms of central sensitization, we considered the five-stage temporal model of central sensitization (TMCS) proposed by Halili [9]. The five stages included 1. phasic activation of the locus-coeruleus noradrenaline (LC-NA) system, 2. salient stimuli; 3. threat coding of salient stimuli; and 4. central sensitization, and 5. neural degeneration. Halili proposed three components that maintain a system in the central sensitization phase: a feed-forward afferent input from dysfunctional visceral input, an adulterated hypervigilant inflammatory response, and oxidative stress in the LC-NA system. Further details are provided in Table 1.

A key element of this model is that central sensitization is preserved by the continuous input of several self-reinforcing loops into the LC-NA system, and that treatment should focus on disruption of these loops.

Halili hypothesized that this disruption could be brought about using three treatment components: temporarily reducing afferent visceral input, shifting humoral inflammatory activity away from the brain and outside the body, and reducing oxidative stress by making oxygenated blood more available around the LC and other stressed areas in the brain. The Systemic Manual Therapy protocols that were proposed to help in the reduction of visceral afferent input are Genito-Urinary-Ovarian-Uterus (GUOU), Barral Abdominal Motility (Barral) and lower-abdominal-urogenital (LAUG). Protocols that shift humoral inflammatory activity away from the brain or completely out of the body

Table 1
5-Stage temporal model for central sensitization.

Stage	Activity	Description	Comments
I	Phasic activation of the LC-NA system	Resting state. No salient stimuli, tonic activation, aberrant afferent input, or oxidative stress	Normal functional state
II	Salient stimuli	Targeted tonic mode activation to allow focus on sensory information or efferent activity	Normal functional state
III	Threat coding of salient stimuli	Wide-ranging tonic activation of efferent and afferent pathways to allow continuing focus as well as response to the stimuli	Normal functional state
IV	Central sensitization	A sustained wide-ranging tonic activation propagates aberrant afferent input and oxidative stress. Less dependent on the original salient stimuli but additional external stimuli can further increase the oxidative stress.	Abnormal functional state
V	Neural degeneration	In susceptible individuals, when the downstream depletion of rate-limiting enzymes causes a cascade of neurochemical destructive reactions	Neuropathological state

include urinary drainage (UD) and diaphragm-cranial sinus (DCS). One protocol that could potentially reduce oxidative stress by making oxygenated blood more available around the LC is Cardiac-Cervical-Cranial-Vascular (CCCV).

The treatment hypothesized to directly influence the environment surrounding the trigeminal system included both DCS and CCCV protocols because they both have a proposed mechanism that has a local impact on that system.

To reject the null hypothesis for central sensitization etiology and treatment, the following four conditions need to be met:

1. This study will have to demonstrate an average improvement in TN and overall symptoms across episodes of care. While improvement across episodes of care does not explain why it occurred, it does indicate that the effects were durable.

2. The protocols associated with the treatment principles for desensitization (reducing afferent visceral input, shifting humoral inflammatory activity away from the brain and outside the body, and reducing oxidative stress) need to be in the group of treatments that are more efficacious than oSOC.

3. At least one of the protocols associated with reducing afferent visceral input (Barral, LAUG, GUOU), and one associated with shifting humoral inflammatory activity (UD, DCS), as well as the CCCV protocol (which is associated with reducing oxidative stress) will be in this group, whether their proposed effects on the reduction of facial pain are direct or not.

4. In addition to improving TN, protocols associated with desensitization needed to be more efficacious than oSOC when assessing overall improvement. This condition is in place because if sensitization is considered a systemic phenomenon and if the treatment indeed improves sensitization, the predicted improvements should occur in more than just one of the patient's complaints.

This hypothesis for CS was previously tested successfully when treating sensitized patients with knee pain [11]. Because DCS and CCCV protocols are anatomically remote from the knee area, their effectiveness treating CS was already demonstrated in that study. Since the remaining protocols (UD, Barral, LAUG, and GUOU) are anatomically remote from the head and face, this study would provide additional validation to the treatment hypothesis proposed in the TMCS that was not possible to obtain in the knee pain paper [11].

3. Direct mechanical or circulatory compromise

To reject the null hypothesis for direct mechanical or circulatory compromise of the trigeminal nerve complex etiology and treatment, the results of the study should have demonstrated that the DCS and CCCV protocols were more efficacious than oSOC.

4. Methodology

This study analyzed fully blinded retrospective clinical data and found no specific patient involvement. Informed consent prior to initiation of therapy.

This study was approved by the Argus Independent Review Board (www.argusirb.com) on July 21, 2021.

To identify which SMT protocols or protocol combinations were more effective than the oSOC, the HPTSAT was used to analyze 41,734 blinded records of 2572 patients from the Halili Physical Therapy EMR (electronic medical records) system v. 2021, Tucson, AZ (HPT2021) between 4/2/2015 and 6/17/2022.

A study sample was created using the search terms "trigeminal," "facial pain," "facial numbness," and "jaw pain" in the patient's PIP list. The resulting sample included 87 patients (71 female and 14 males; average age 60.74, age range, 12–95 years). Two patients were excluded from the analysis because although they had PIP of TN, they did not have any TN symptoms during the study period.

Among the 85 patients, there were 105 episodes of care (if 90 days had passed since the last visit, then the next visit was considered a new episode of care). Eighty-two episodes were treated with chronic presentation (duration >3 months) and 23 episodes with acute onset. Among the related medical diagnoses, 12 had Bell's palsy (BP), nine had Ramsay Hunt syndrome (RHS), 19 were previously diagnosed with TN, six had facial trauma, two had a cerebrovascular accident (CVA), one patient had a tumor removed and one developed symptoms after dental work. The remaining patients had no related diagnosis of facial or jaw pain or PIP complaint. Gabapentin was used for pain control during 15 episodes of care, and pregabalin was taken in eight.

HPTSAT located and analyzed 99 SMT protocols or protocol combinations (with a frequency >5). In this group, the tool identified the protocol and protocol sequences that met or exceeded the differentiation criteria discussed in the introduction. Further qualitative demographic and comorbidity information as well as episode of care data were compiled and analyzed using HPTSAT and MedCalc software [22].

5. Results

To gain a qualitative understanding of several aspects of the sample, such as uniformity, effects of comorbidities, specific changes, and overall changes in patients' PIP over the study period, we noted the following: the average period a patient was followed in this study was 390 days. The average length of episodes of care was 180 days (95 % CI 139–221), the average number of visits per episode was 18 (95 % CI 14–22), and the average number of days between treatments was 10 (95 % CI, 8–12). One-way analysis of variance (ANOVA) indicated no statistically significant difference ($p = 0.35$) between the related medical diagnosis groups (BP, RHS, TN, CVA, and facial pain group without related diagnosis). There was no statistical difference in outcomes between patients taking gabapentin ($p = 0.72$) or pregabalin ($p = 0.89$) and patients not taking these medications. No statistical difference was noted for sex ($p = 0.67$) or age ($p = 0.89$). For a full list of comorbidities and additional information including the performance of all the other protocols and sequences tested, please refer to the accompanying dataset [10].

Changes in the overall PIP scale scores over the study period were as follows: 65 patients (76 %) reported improvement in overall PIP complaints, 6 patients (7 %) either did not record or reported no change, and 14 patients (16 %) reported worsening of overall PIP scores. On an average, the overall PIP scale score improved by 12.01 points (p, STD, and 95 % CI were < 0.001, 18.28, 15.9, and 8.12, respectively). This change exceeded the MCID of 3.8, including the 95 % CI upper limits of 8.2 points.

Specific changes related to TN complaints were as follows: 56 patients (66 %) reported improvement, 15 patients (18 %) either did not record or reported no change, and 14 patients (16 %) reported worsening of the facial symptoms score. On average, individual complaints of facial symptoms improved by 1.88 points (p, STD, and 95 % CI were < 0.001, 2.65, 2.44, and 1.32, respectively). This change exceeded the MCID of 0.89, including the 95 % CI upper limit of 1.4 points.

Of the 99 protocol combinations assessed, 13 combinations containing eight distinct protocols passed the HPTSAT criteria to demonstrate a better treatment effect than the oSOC for the specific TN complaint. Sixteen combinations, including seven of the eight protocols identified as effective in the individual complaint group, passed the criteria for better than oSOC for overall improvement. The passing combinations are listed in Table 2.

The eight individual protocols passing the HPTSAT criteria were VTCP (Venous-Thoracic-Cardiopulmonary), UD, DCS, LAUG, CCCV, SYMPN (Sympathetic Nerve protocol), Barral, and Barral-CVVT (Barral abdominal motility protocol combined with Cardiovascular-Venous-Thoracic protocol). All but one of the protocols (SYMPN) that passed the HPTSAT criteria for TN were also found in the combinations that passed the criteria for effectiveness on overall change.

In accordance with the TMCS for central sensitization [9], six of the

Table 2
Passing combinations.

Part one: results by individual score for facial pain complaint

Protocol/combinations	n	freq, control	ARC5	Rx, oSOC	SD (95 % CI)	Welch	MW	ANOVA	Hedges' g
CCCV VTCP	21	197, 8744	0.79	0.92, 0.13	1.65 (1.88–1.42)	< .001	< .001	< .001	0.58
BARRAL CCCV SYMPN	20	112, 8829	0.74	0.88, 0.14	1.74 (2.07–1.42)	< .001	< .001	< .001	0.54
CCCV SYMPN	24	217, 8724	0.69	0.82, 0.13	1.64 (1.86–1.42)	< .001	< .001	< .001	0.51
UD DCS BARRAL CCCV	51	133, 8808	0.61	0.75, 0.14	2.25 (2.64–1.87)	0.003	0.001	< .001	0.43
DCS BARRAL CCCV	57	304, 8637	0.47	0.61, 0.14	2.02 (2.25–1.8)	< .001	< .001	< .001	0.35
SYMPN	41	539, 8402	0.47	0.59, 0.12	1.61 (1.74–1.47)	< .001	< .001	< .001	0.34
UD DCS BARRAL	54	267, 8674	0.44	0.58, 0.14	2.11 (2.37–1.86)	< .001	< .001	< .001	0.32
BARRAL-CVVT	25	308, 8633	0.39	0.53, 0.14	1.6 (1.78–1.43)	< .001	< .001	< .001	0.29
DCS Barral	60	516, 8425	0.36	0.49, 0.13	1.94 (2.11–1.78)	< .001	< .001	< .001	0.27
CCCV LAUG	21	198, 8743	0.35	0.49, 0.14	1.84 (2.1–1.58)	0.008	< .001	< .001	0.26
Barral CCCV	79	704, 8237	0.35	0.47, 0.12	1.75 (1.88–1.62)	< .001	< .001	< .001	0.25
Barral	88	1147, 7794	0.31	0.42, 0.11	1.63 (1.73–1.54)	< .001	< .001	< .001	0.23
CCCV UD DCS	32	165, 8776	0.3	0.45, 0.15	1.69 (1.95–1.43)	0.022	0.024	0.004	0.22

Part two: results by PIP scale

Protocol/combinations	n	freq, control	ARC5	Rx, oSOC	SD (95 % CI)	Welch	MW	ANOV	Hedges' g
UD DCS BARRAL CCCV	51	133, 8808	4.75	5.78, 1.03	11.18 (13.08–9.28)	< .001	< .001	< .001	0.74
UD DCS BARRAL	54	267, 8674	3.83	4.81, 0.98	10.31 (11.55–9.07)	< .001	< .001	< .001	0.6
CCCV VTCP	21	197, 8744	3.63	4.65, 1.02	7.08 (8.07–6.09)	< .001	< .001	< .001	0.56
DCS CCCV	47	360, 8581	3.28	4.25, 0.97	10.57 (11.66–9.48)	< .001	< .001	< .001	0.51
DCS BARRAL CCCV	57	304, 8637	3.05	4.05, 1	10.16 (11.3–9.01)	< .001	< .001	< .001	0.48
DCS Barral	60	516, 8425	2.73	3.67, 0.94	9.53 (10.35–8.71)	< .001	< .001	< .001	0.42
CCCV UD DCS	32	165, 8776	2.47	3.52, 1.05	10.57 (12.18–8.96)	0.003	< .001	< .001	0.38
Barral	88	1147, 7794	2	2.84, 0.84	8.71 (9.21–8.21)	< .001	< .001	< .001	0.31
CCCV UD	55	477, 8464	2	2.99, 0.99	8.43 (9.18–7.67)	< .001	< .001	< .001	0.31
Barral CCCV	79	704, 8237	1.8	2.76, 0.96	8.45 (9.08–7.83)	< .001	< .001	< .001	0.28
BARRAL-CVVT	25	308, 8633	1.78	2.82, 1.04	9.56 (10.62–8.49)	0.001	< .001	< .001	0.28
CCCV LAUG	21	198, 8743	1.77	2.83, 1.06	8.7 (9.91–7.48)	0.005	0.006	< .001	0.27
UD DCS	138	1066, 7875	1.66	2.56, 0.9	9.6 (10.18–9.03)	< .001	< .001	< .001	0.26
VTCP UEDJ	25	211, 8730	1.62	2.68, 1.06	7.31 (8.3–6.32)	0.002	< .001	< .001	0.25
SLMG separated	32	367, 8218	1.43	2.5, 1.07	6.34 (6.99–5.69)	< .001	< .001	< .001	0.22
CCCV DCS	47	398, 8543	1.37	2.41, 1.04	6.83 (7.5–6.16)	< .001	< .001	< .001	0.21

Key: **n**: number of times combination was done; **freq**: number of 1–5 measurements including this combination; **control**: number of 1–5 measurements not including this combination; **ARC5**: average rate of change over five measurements; **Rx**: ARC5 of freq; **oSOC**: ARC5 of optimal standard of care (control frequency); **SD**: standard deviation; **CI**: confidence interval; **Welch**: *p* of Welch's t test; **MW**: *p* of Mann-Whitney test; **ANOVA**: *p* of Analysis of variance; **Hedges' g**: Hedges's g effect size; **LAUG**: Lower Abdominal Urogenital; **Barral**: Barral Abdominal Motility; **UD**: Urinary Drainage; **DCS**: Diaphragm Cranial Sinus; **CCCV**: Cardiac Cervical Cranial Vascular; **VTCP**: Venous Thoracic Cardiopulmonary; **CVVT**: Cardiovascular Venous Thoracic; **SLMG**: Side-Lying Modified Glides; **SPDJ**: Spinal Drainage Jones (all versions); **SYMPN**: sympathetic nerve.

eight passing protocols (UD, DCS, CCCV, Barral, Barral-CVVT and LAUG) were performed because of their hypothesized general effect on central sensitization. Two of these protocols (CCCV and DCS) could have an additional, more direct effect on the trigeminal nerve.

Although the VTCP protocol is not discussed in the TMCS, its beneficial effects noted both for the overall PIP scale and specifically for TN are consistent with the model's suggested strategy for reducing afferent visceral input. This is because this protocol also targets a portion of the visceral system (cardiac and pulmonary systems).

The only protocol that seemed to benefit from the TN complaint without a strong desensitization effect on the overall PIP scale was SYMPN. When we examine the effect size for SYMPN, the Hedges' g score for the overall PIP scale was only 0.02 ($p = 0.68$) while the Hedges' g score was 17 times bigger at 0.32 ($p < 0.001$) on the individual TN complaint. This effect is feasible because anatomically, several individual SYMPN techniques are performed in the vicinity of the trigeminal system and can normalize neuronal activity in the spinal trigeminal nucleus [24,27].

6. Discussion

As indicated in the introduction, by using the combined HOAC-APD model, we were able to accomplish several items: establishment of an oSOC based on our historical treatment data, identification of several interventions that are distinguishably better than that standard, and fortification of the TMCS hypotheses for both pathology and treatment of TN.

Qualitatively, the episode of care data is a measure of the effectiveness of the decision-making process in the HOAC model. This data cannot tell us why the patients have gotten better, but because of the good uniformity and minimal influence of co-variants noted in this sample, we can use it as a reasonable estimation of the best available standard of care. For example, if a future patient with TN asks for a prognosis, we can consider the findings of this study that 66 % of the patient had gotten significantly better, that it took about 18 visits and approximately 6 months.

Using the findings of this study, in future treatments, we can focus on the eight protocols found to be better than the current oSOC. We expect that, because of the heavier integration of these eight protocols, a future repeat analysis should yield an even better standard for episodes of care outcomes.

Upon analysis of our HOAC hypothesis for pathology and treatment, it was found that the results of this study met the four conditions (presented in the introduction) required to reject the null hypothesis and support the TMCS hypothesis for central sensitization.

There was a significant improvement in episodes of care, which met the first condition. The second condition was met by the following, which were all found to be more effective than oSOC: protocols associated with the reduction of visceral input (LAUG, Barral, Barral-CVVT and VTCP); protocols shifting humoral inflammatory activity (UD, DCS), and CCCV protocol, which is associated with reduced oxidative stress. These protocols were found to be more effective than oSOC, regardless of whether they had a proposed direct effect on TN, which meets the third condition. Finally, all these protocols also passed the HPTSAT criteria, requiring them to be better than the oSOC when looking at the overall effects on the PIP scale, meeting the fourth

condition.

The accompanying hypothesis that intervention should also be accomplished by using protocols that directly affect the trigeminal system is supported by the improvement noted when using the SYMPN protocol since this protocol did not appear to have a strong overall effect on the PIP scale. The two protocols, CCCV and DCS, should both be used in treatment regardless of whether the benefit works directly on the trigeminal system, overall sensitization, or both. The reason for this is that in this study (which hypothesizes their direct effect on the trigeminal system), it is not possible to isolate their direct effects on systemic central sensitization.

Finally, two general assertions were made in the introduction: the first is that treatment focus should consider not only the mechanism of injury but also why the problem is not getting better, and the second is that treatment should focus on removing the barriers that prevent the body from healing itself. Both seem to be reinforced by the findings of the present study. The most significant improvement occurred when central sensitization was targeted in the treatments and not when the facial region was directly manipulated. The TMCS is a function of time and trauma; the longer a system is traumatized, the worse everything gets, and over time, traumatized systems tend to become stuck in that state. Our study demonstrated that when we intermittently disrupted trauma-caused self-reinforcing loops, we removed some of the obstacles needed for recovery.

7. Limitations

- We need to consider that most patients seek help for multiple problems, not just for TN. Therefore, until we have outcome data for multiple other problems that are similar to those of this study and until we understand how each problem interacts with any other problems present, the treating physical therapist must still rely on the basic HOAC qualitative model when developing an individual plan of care.
- In this study, we established with statistical certainty that DCS and CCCV protocols are effective in treating both TN and overall symptoms. However, because of the possibility that the effectiveness of these protocols was due to a direct effect on the trigeminal system, we could not quantify their effects on central sensitization. This quantification will have to happen when studying conditions such as knee pain, for example, where neither of these protocols has a proposed direct or regional effect on the primary problem.
- We need to be cautious in interpreting the meaning of the observation that there were no statistical differences between the group that was taking Gabapentin or Pregabalin ($p = 0.72$ and 0.89, respectively) and the group that did not take these medications. All comorbidity analyses were performed over episodes of care and not by measuring the difference in ARC5 when the medications were present or absent; therefore, we can say that the efficacy of the intervention (i.e., physical therapy) did not change one way or another due to the presence of these medications.
- We can tell that as a group there was overall statistically significant improvement over episode of care; however, because only 14 patients had reported worsening of TN symptoms, and even a smaller subgroup (six patients) had reported worsening of symptoms to a degree greater than 1 point, it was not statistically possible to isolate the reasons and answer the important question of why TN worsened in this group.
- The study sample did not show sufficient variability in the order in which the sequence of protocols was performed. Therefore, we cannot make statistical inferences regarding the optimal order of protocols in a sequence.
- The absence of randomization when selecting patients or protocols introduces bias, considering confounding variables such as differences in age, gender, duration of symptoms, or concurrent conditions were not adequately accounted for. This might limit the generalizability of the findings, making it difficult to conclude that the observed effects were due to SMT alone.

8. Conclusion and generalizability

This study demonstrated that a complicated problem, such as TN, can be effectively treated by focusing on central sensitization. It also illustrates how a problem can be addressed by removing the barriers to healing.

The results of this study support the hypothesis expressed in the TMCS, suggesting that central sensitization can be treated by creating intermittent interruptions in the self-reinforcing loops that sustain it. This is illustrated by the observation that the strategy to address the three treatment elements of the TMCS for desensitization (reducing afferent visceral input, shifting humoral inflammatory activity away from the brain and outside the body, and reducing oxidative stress) using protocols hypothesized to do so (Barral, LAUG, UD, DCS, CCCV) yields outcomes that are better than the oSOC.

Furthermore, by including standardization of care, continuous use of outcome tools, and control of internal validity using appropriate statistical analysis strategies, this model can be further developed into a potent clinical research tool.

This study's findings can be generalized in two ways. First, clinicians who use SMT, fascial counterstrain, IMT or Barral techniques can immediately implement the SMT protocols suggested in this study. The episode of the care outcome is the second generalization that can be made. This outcome can be considered by any professional who treats TN and is used as a benchmark against which all other interventions can be measured.

9. Recommendation for future research

To overcome the limitations of this current study, future research should be structured as a randomized controlled trial (RCT) with a prospective study design, where data is collected in real-time allowing for better control of variables and more reliable data collection.

Ethical approval

This study was approved by the Argus Independent Review Board (www.argusirb.com) on July 21, 2021.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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Glossary

HOAC: The Hypothesis-Oriented Algorithm for Clinicians (HOAC) model [20,21] is a clinical evaluation tool which includes several elements. This process results in several complementary (or competing) hypotheses that include theories for both etiology and the basis for intervention, as well as a treatment plan that includes these interventions. The second part of the HOAC model calls for periodic reassessment of both the existing hypotheses and the effectiveness of treatment, and the continuous synthesis of new hypotheses and interventions. The two hypotheses tested in this study are that symptoms are caused via a direct mechanical or circulatory etiology and/or central sensitization in accordance with the temporal model for central sensitization (TMCS) [9]

PIP scale: The patient identified problem scale (PIP) [6] is a validated self-reporting outcome measure designed to quantify the assessment and reassessment process under the HOAC model

APD: The APD model was initially introduced during the Ebola outbreak in 2014 [18] to allow for a faster evaluation of new emerging therapies by comparing multiple interventions against the existing optimal standard of care (oSOC). Once an intervention is found to be better, it is incorporated into a new oSOC, to which all new interventions are compared.

oSOC/ New oSOC: In the context of this study, the optimal standard of care (oSOC) refers to the interventions used **prior** to completion of the investigation. The new oSOC refers to the interventions to be used **after** completion of the study and would include additional interventions which were found to be effective in this study. In accordance with the APD, future investigation will consider the new oSOC as the basis in which new interventions will be compared to.

HOAC/APD: The HOAC/APD combines model refers to application of the **clinical** HOAC model in the quantitative **research context** of the APD model. This is accomplished by using the standardized SMT protocols, a validated outcome tool (PIP scale) and a statistical analysis tool (HPTSAT) that controls for the internal validity challenges common in a retrospective analysis.

TMCS: The temporal model for central sensitization (TMCS) [9], is a comprehensive model for central sensitization describing in detail the neurophysiology involving the central and autonomic nervous systems. The model describes several neurological loops that are propagating CS as well as a hypothesis for treatment and a test for the hypothesis involving meeting prespecified conditions. This study uses this specific testing scheme to test the viability of the treatment of central sensitization in patients with facial pain.

Direct mechanical or circulatory compromise: Direct mechanical or circulatory compromise of the trigeminal nerve is an alternative (competing or complementary) hypothesis tested in this study.

Hypotheses testing: The hypothesis test for the proposed mechanism and treatment of the CS component of facial pain is detailed in the TMCS paper and contains several conditions to be met including demonstrating that several SMT protocols (UD, DCS, Barral, LAUG, GUOU and CCCV) are found to be more effective than the oSOC both for facial pain and overall symptoms. if two of these protocols (CCCV and DCS) has direct effects over the head, the direct mechanical or circulatory compromise hypothesis cannot be rejected and should be considered as complementary one to the TMCS

SMT protocols and protocol sequences: Systemic Manual Therapy (SMT) protocols [5] are a group of about 50 protocols that have been developed and standardized over the past few decades by incorporating individual techniques from several osteopathic and physical therapy methods, such as fascial counterstrain (FCS) [26], Barral [1], integrative manual therapy (IMT) [4] and muscle energy techniques (MET) [16]. A **protocol** refers to a specific group of techniques that are performed in one treatment session. in the medical records a protocol is referred to by a group of letters (UD or DCS or CCCV etc.). Unless specified otherwise in the treatment record, a protocol is done in the exact same manner for each treatment. Prior work [7] quantified the ability to achieve standardization in performance between trained treating clinicians. A **protocol sequence** refers to a series of protocols performed over several consecutive treatment sessions.

HPTSAT and ARC5: The Halili physical therapy statistical analysis tool (**HPTSAT**) [8] is a software tool designed to control for number of internal validity threats, such as repeated measurements error, when retrospective clinical data is analyzed. One of the key functions of the tool is to measure the average rate of change (**ARC5**) during multiple treatment sessions. The tool then compares the rate during a period a specific protocol or protocol sequence was done and compares it to the rate during times other treatments were done. The tool identifies all protocols or sequences that met a specific quantitative differentiation criterion. The criterion uses both parametric and non-parametric tests as well as sample and effect size.