

EFFECTS OF HIGH DOSE CAPSAICIN ON FACIAL PAIN PERCEPTION

By

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This is dedicated to my wife, my parents, and my children, who have reaffirmed God's love and our (man's) purpose in life.

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A significant number of individuals suffer chronic pain associated with temporomandibular joint disorders (TMD); however, there still remain questions regarding the underlying pain mechanisms associated with TMD and therefore treatment strategies can be unclear. The transient receptor potential channel, vanilloid subfamily member 1 (TRPV1) has been identified as a target for pain control as it is expressed primarily on pain neurons and is involved with mediating inflammatory pain. Capsaicin, a TRPV1 agonist both activates and inactivates TRPV1-expressing neurons without producing tissue damage. A double-blinded, placebo-controlled clinical trial was used to investigate two specific aims: (1) To evaluate if chronic TMD patients modulate pain differently than normal control subjects; (2) To evaluate the analgesic efficacy of capsaicin in chronic TMD patients. Our results indicate that capsaicin significantly increases experimental pain in both TMD and non-TMD groups as compared to vehicle in the short term but shows a decrease of TMD pain in the week following . It has no effect on pressure pain threshold but it does decrease thermal pain threshold two hours after application though not one week out.

CHAPTER 1 INTRODUCTION

Background

Orofacial pain disorders are estimated to affect 20% of the U.S. population [1] and are made up largely of temporomandibular joint disorders (TMD). Estimates of the prevalence of painful TMD range from 3.6% to 7% [2; 3] with women being affected more frequently than men by almost a two to one margin [1; 4]. A brief review of capsaicin's role in pain research will provide some understanding as to why capsaicin may lead to an effective TMD pain treatment.

Capsaicin and the Vanilloid Receptor TRPV1

Capsaicin is a lipophilic vanilloid compound [5] that may lead to a novel analgesic drug that does not use the cyclooxygenase pathway or opioid receptors [6]. Research has allowed the capsaicin receptor to be isolated, identified, and, in 1997, cloned [7]. The capsaicin receptor belongs to a nonselective, cation (sodium/calcium), ligand gated ion channel family named transient receptor potential channel, vanilloid subfamily member 1 (TRPV1). It is involved in nociception, inflammation and in sensory signaling [8-10]. The receptor responds to protons, temperatures greater than 43°C, and a number of vanilloid agents including capsaicin [11-13]. Additionally, TRPV1 is primarily expressed by A δ and C-fibers of afferent neurons which are, in part, responsible for the erythema, burning sensation, and sensitivity to other stimuli after application of capsaicin.

In addition to studying the molecular biology, capsaicin has been clinically used and tested. A study involving subjects applying capsaicin 0.075% four times daily for three weeks demonstrated a degeneration of epidermal nerve fibers (ENF) by approximately 80% mostly at the epidermis [14]. Noting this effect, Malmberg et al. compared the effectiveness of low dose

capsaicin (0.04% w/w) to a high dose (8% w/w) topically applied for set intervals up to 120 minutes. They found that the low dose had no effect on reduction of ENF nor reduction on heat sensitivity when compared to placebo. Yet, after a single dose of 8% capsaicin there was a reduction of ENF and desensitization to heat stimuli that were seen a week out [15].

The expectation of TRPV1 is that it could be a target for pain control [8], and if realized, a novel therapeutic approach inhibiting certain nociceptive neurons while maintaining other motor and sensory functions [10].

Capsaicin Utility

Studies indicate that capsaicin may have some analgesic value when applied topically at low doses (0.025% to 0.075%). It has shown some efficacy for treatment of chronic pain disorders such as rheumatoid arthritis (RA) and osteoarthritis (OA) [16; 17]. Two studies have shown favorable results for patients suffering post herpetic neuralgia (PHN) [18; 19], and capsaicin is the only drug labeled by the FDA for PHN. Questioning the presumed efficacy of low dose capsaicin is a meta-analysis of previously published trials, which concluded that it had moderate to poor efficacy when treating chronic neuropathic or musculoskeletal pain [20].

Only one study has investigated the potential benefit of capsaicin, albeit low dose, as a treatment for TMD. This randomized, double-blind, placebo controlled trial showed no difference in reduction of symptoms between the 0.025% capsaicin and placebo groups suffering from TMD [21].

Significance

The findings from previous OA and RA studies engender some hope in treating TMD, which also has a joint pain component, with capsaicin by targeting TRPV1, as it plays a role in

inflammation and pain. The literature, though, has many studies questioning capsaicin's analgesic effectiveness at low doses and there are no well controlled analgesic studies of 8% capsaicin. With only one study evaluating capsaicin's resolution of TMD pain, albeit low dosing, there is a definite need to explore the effects of higher dose topical capsaicin in well-controlled, randomized trials before conclusions can be drawn about targeting TRPV1 as an effective method for controlling TMD pain and ultimately chronic pain.

Hypothesis and Specific Aims

We proposed a double-blind, placebo-controlled clinical trial to investigate two specific aims: (1) To evaluate if chronic TMD patients modulate pain differently than normal control subjects; (2) To evaluate the analgesic efficacy of capsaicin in chronic TMD patients. We hypothesized that patients suffering from TMD will rate pain higher than control subjects following capsaicin application and TMD patients that receive capsaicin treatment will have a significant reduction in their pain compared to those receiving vehicle treatment.

CHAPTER 2 METHODS

Subject Recruitment and Randomization

Study protocols followed the guidelines of the Institutional Review Board of the University of Florida. The targeted study group was those that suffer from TMD and healthy, control subjects (referred to as “non-TMD subjects”) that were identified through advertising within the greater Gainesville, FL region. Treatments were randomly assigned via a random number generator and syringes were labeled with a study protocol number (protocol number designated active versus vehicle but still unknown to investigator or participant). All participants received compensation for their time.

Inclusion Criteria

Normal, healthy, female volunteers, age 18-65 years of age, American Society of Anesthesiologists (ASA) status 1 or 2, and deemed in good general health were recruited. This represents the age range of many chronic pain patients, including patients with TMD, and the exclusive gender was selected since there are a higher proportion of females (>2:1 female: male) that develop TMD.

In addition to the same age and gender requirements, the TMD patients’ inclusion criteria also required subjects to have TMJ pain of greater than six months duration, who rated their pain a three or greater for the week that immediately preceded the initial testing date, and meeting the Research Diagnostic Criteria (RDC), Group IIIa. Arthralgia of the temporomandibular joint (TMJ) [22]. The last criteria is met if they have no crepitus, and must have verified joint pain with palpation at either the lateral pole or at the posterior attachment and meet one of the

following: Be able to point to either muscle or joint pain, joint or muscle pain on assisted/unassisted opening, or joint or muscle pain in right or left excursive movements.

Exclusion Criteria

Exclusion criteria are as follows: an ASA status 3-5, pregnant or breast-feeding mothers, allergy to investigational drugs or to red chili peppers, presence of chronic disease (e.g. cardiovascular disease, liver disease, kidney disease, diabetes, etc.). Subjects with course crepitus of the TMJ or any subjects who had taken any pain medications, either over the counter or prescription, within 48 hours prior to participating in the trial for either testing day were also excluded. Excluded medications included but were not limited to aspirin, ibuprofen, acetaminophen, hydrocodone, or steroids. No exclusions were made based on race, gender, or religion.

General

Once the subject had the study explained and signed the Informed Consent form, they were then asked to complete a health history questionnaire and the Research Diagnostic Criteria (RDC) for Temporomandibular Disorders History Questionnaire. The subjects were also informed that they could stop participating in the study or have the cream removed at any point. If they asked for removal of the cream earlier than the designated time, then the current time was noted, and they were then given the option to continue with the rest of the study or stop all together. Blood pressure, temperature, results of pregnancy test, and visual analogue scale (VAS) and verbal ratings of that day's TMD pain were recorded initially prior to any testing.

Quantitative Sensory Testing

Quantitative sensory testing (QST) which includes heat and pressure pain threshold were completed for both normal and TMD subjects prior to drug application (baseline), two hours

post-drug application, and at the second visit one week later. All QST was practiced on the non-dominant arm to acclimate the subject to the testing procedures.

Pressure Pain

A clinical grade pressure algometer (FPX 50--25 x 0.2N Wagner, Greenwich, Ct), which has a rubber tip, measured pressure pain threshold by placing the probe tip perpendicular to the skin testing site and applying pressure in an increasing manner at a rate of 1Kg/sec. The subject signified the time of first painful response, at which point the pressure application ceased and the value recorded. The TMJ (site 1) and masseter (site 2) on both the right and left sides of the face were evaluated. After testing both sites bilaterally, VAS ratings of global pain were immediately recorded. Global pain was defined as clinical (TMD) pain plus experimental pain. This test was repeated three times unless two of the three tests were not within 0.5 Kg necessitating a fourth trial.

Thermal Testing

Changes in thermal sensitivity were assessed using Medoc Thermal Testing Device (Medoc Advanced Medical Systems, Durham, N.C.). Pain threshold was assessed using an ascending method of limits with a rate of rise equaling 0.5 °C/sec., starting at 32°C. and not to exceed 53°C. The thermode as applied on the skin overlying the masseter area and TMJ. Subjects indicated by pressing a button when they first felt pain immediately stopping the stimulus and the value was recorded. After applying the heat to the first side of the face, a two and a half minute timer was started and then the heat probe was applied to the opposite side of face as before. At the sound of the timer a pain VAS reading was taken. A fourth trial was required if two of the three trials' recorded temperatures were not within 1°C.

Drug Application

Formosa Laboratories supplied the capsaicin (Taoyuan, Taiwan), with the final 8% topical cream used was compounded by Westlab Pharmacy (Gainesville, FL). The control (vehicle) cream was the same topical solution but contained no capsaicin.

The investigator applied 0.1ml cream to a 3 cm² area overlying the affected TMJ and superficial masseter to be left on for two hours. The drug was applied to the right or left side randomly for subjects without TMD, whereas, for the TMD sufferers, the side that was more painful was studied. During the application the patient rated what their expected pain levels would be with the given treatment and also their desire for pain relief. Capsaicin-evoked pain intensity VAS ratings were collected every five minutes for the first half hour of the experiment; then every thirty minutes for the duration of the two hours. At the end of the two hours, the subject's face was wiped clean with soaked gauze of half and half cream followed by alcohol swabs to remove residual capsaicin.

After removal of the cream the battery of tests was repeated and patient dismissed. All subjects were phoned twenty four hours following the cream application to assess pain and adverse event experience. Furthermore, TMD patients rated their clinical pain for seven days using a VAS home diary and returned it on their second visit. The one week follow up consisted of performing the same QST followed by the RDC for Temporomandibular Disorders Physical Assessment (Axis I). The physical exam was completed by the Principal Investigator and included standard evaluation of the TMJ and masticatory muscles. Pain ratings were recorded for each of these palpation sites.

Measures

Perceived pain intensity, desire for pain relief, and expected pain levels were measured using a slide algometer VAS [23] following capsaicin or vehicle cream application. In using the pain sensation intensity scale the patient would slide the middle sliding part of the device to the right for an indicator of greater pain sensation intensity. The arrow at the extreme left meant no pain sensation at all and the arrow at the extreme right indicated a pain sensation intensity that subject imagined to be the most intense that she could possibly experience. Similarly, sliding algometer VAS was used as the desire for relief scale, with the arrow at the extreme left meaning no desire for pain relief and the arrow at the extreme right representing the most intense desire for relief imaginable. Lastly, ratings of expected pain level were anchored by the descriptors “no expected pain” on the left and “the most intense pain imaginable” on the right. These scales for expected pain levels, desire for pain relief and anxiety have been validated previously [23-25].

CHAPTER 3 RESULTS

Initial Controls' Results

Demographics

Initially 44 control (non-TMD) subjects were recruited with 21 receiving capsaicin and the remaining 23 received vehicle. An additional 10 capsaicin non-TMD subjects were recruited to evaluate the effects of capsaicin on QST performed one week later. Sixteen TMD subjects were recruited with eight receiving capsaicin and the remainder the vehicle. None of them dropped out but two participants (one from each of the TMD and non-TMD capsaicin groups) requested the cream to be removed prematurely (before the two hour time limit) after drug application though they chose to participate in the remainder of the study. Their data was not included in the results. [Table 3-1](#) summarizes the total number of subjects enrolled to date tabulated by age and [table 3-2](#) by race excluding the two participants who did not complete all requirements.

Experimental and Global Pain

Application of capsaicin increased pain ratings as compared to vehicle-treatment in both healthy and TMD symptomatic subjects ([Figure 3-1](#)). When we evaluated the short-term effects of capsaicin versus vehicle treatments (up to 2 hours post-application) for the TMD and non-TMD groups, we found there was a significant increase in VAS ratings over time for the capsaicin treated group as compared to vehicle treated subjects (ANOVA, $P < 0.001$).

Individual subjects who were assigned to control and treatment group provided multiple repeated observations for subjective pain measurements during 5, 10, ..., 120 minutes and later, 1 to 7 days. Because the serial measurements and distinction between relatively short-term

versus long-term effects were correlated according to the individual subjects, multilevel (hierarchical) linear model (=mixed model) was applied. This linear mixed model has some advantages: 1) does not require observations to be independent with constant variance; 2) can test the variability of individual subject's random effect; 3) some missing measures do not cause all data for an individual subject to be ignored. TMD groups' global (TMD) pain rating at initial time point (prior to any QST) and seven days post-treatment. The VAS measures during 5 to 120 min were significantly lower in the control vehicle group than in the capsaicin treatment group ($P = 0.002$). The VAS measures during 5 to 120 min were decreased over time ($P < 0.001$). The VAS measures during 1 to 7 days (Figure 3-2.) were significantly greater in the control vehicle group than in the capsaicin treatment group ($P = 0.001$). The VAS measures during 1 to 7 days showed an unknown tendency over time due to inadequate sample size ($P < 0.001$). The pattern of VAS measures was reversed in case of capsaicin treatment in the long run ($P = 0.033$).

Thermal Pain Threshold

Capsaicin and vehicle TMD groups have similar baseline thermal pain thresholds and this comparison holds true for the Non-TMD's groups. Both TMD and non-TMD groups (Figure 3-3A and B respectively) demonstrated a significant decrease in thermal pain threshold (-3.5°C and -5.4°C respectively) (Paired T test, $p < 0.05$) at two hours post-capsaicin cream application. The thermal threshold recovered to baseline levels by one week, with no differences noted when compared to baseline values for either group. No significant thermal pain threshold differences were observed at any time of the post-vehicle test sessions (+2 hr, 1 week) as compared to baseline levels (Figure 3-3A and B). Comparison of results for non-TMD's one week follow up

(n=10) were compared to their own baseline average rather than the combined data of all capsaicin non-TMD subjects (n=30).

Pressure Pain Threshold

Both TMD and non-TMD subjects showed similar pressure pain thresholds respectively across time at baseline at both the masseter and the TMJ. No significant changes in pressure pain threshold across time emerged for non-TMD or TMD subjects (Figure 3-1 A and B, respectively) regardless if they received vehicle or capsaicin treatment as compared to baseline. Capsaicin TMD subjects (n=8) had a significantly lower threshold of 2.01 ± 0.08 g (mean \pm s.e.m., $p < 0.05$) as compared to non-TMD controls (n=10) at 2.59 ± 0.73 g at QST baseline.

Table 3-1. Age distribution

Treatment	Subject	Normal			TMD		
	N	Mean	SD	N	Mean	SD	
Control vehicle	23	22.5	6.9	8	25.8	12.2	
Capsaicin 8%	30	28.0	10.6	7	29.3	12.3	
Total	53	25.6	9.5	15	27.4	11.9	

Two-way (2-factorial) ANOVA revealed that there is no significant difference in the age distribution neither between normal versus TMD subjects ($P = 0.437$), nor between control versus treatment groups ($P = 0.127$).

Table 3-2. Ethnic distribution

Ethnicity	Normal subjects			TMD patients		
	Control	Capsaicin 8%	Total	Control	Capsaicin 8%	Total
Caucasian	12 (52.2)	20 (66.6)	32 (60.5)	5 (62.5)	5 (71.4)	10 (66.6)
African-American	2 (8.7)	2 (6.7)	4 (7.5)	-	1 (14.3)	1 (6.7)
Hispanic	8 (34.8)	5 (16.7)	13 (24.5)	3 (37.5)	1 (14.3)	4 (26.7)
Asian	1 (4.3)	3 (10.0)	4 (7.5)	-	-	-

Fisher's Exact statistic showed that there is no significant difference in the ethnicity distribution neither between normal versus TMD subjects ($P = 0.459$), nor between control versus treatment groups ($P = 0.569$). Percentages are in the parentheses.

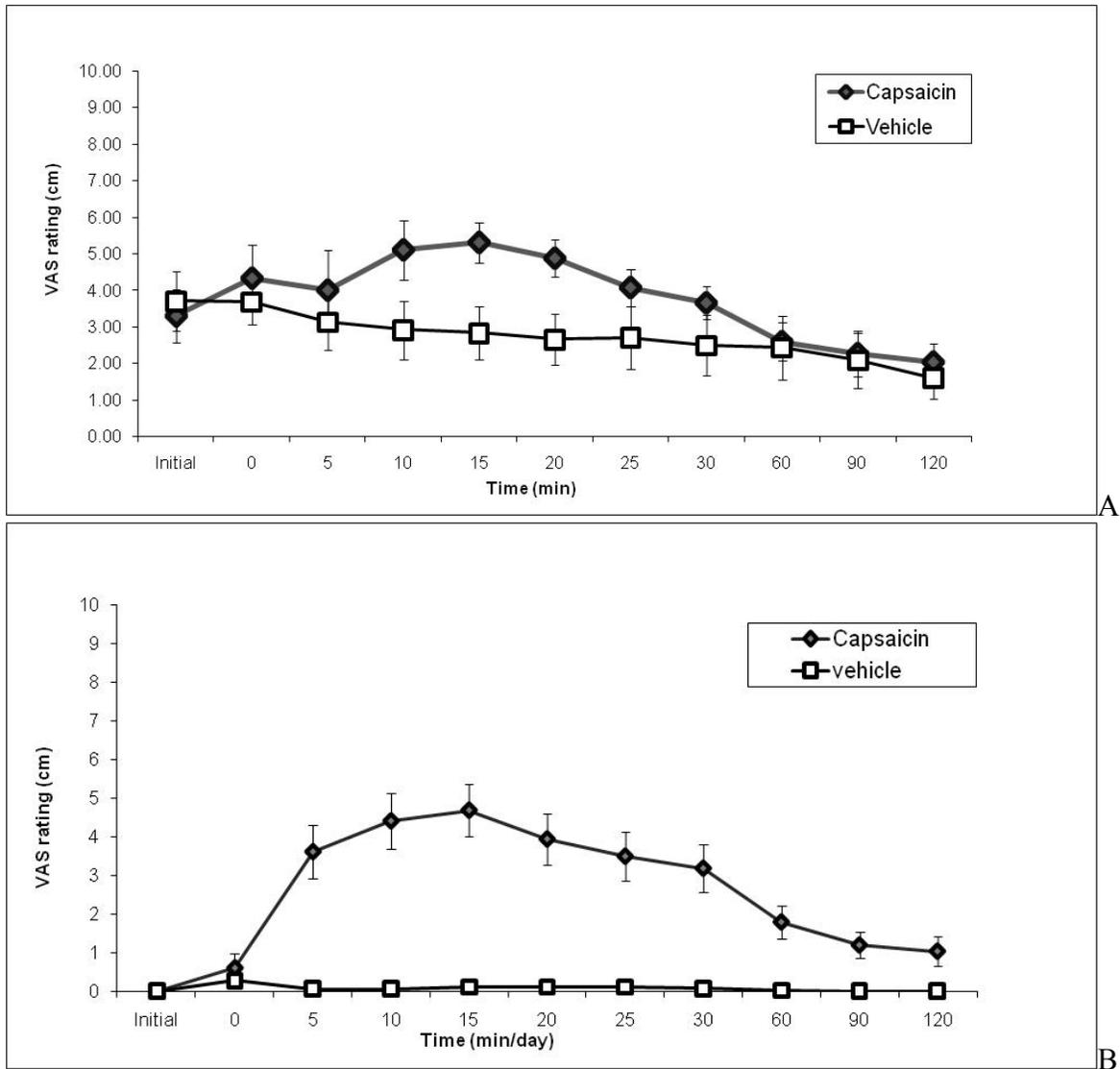


Figure 3-1. Global pain ratings. A)TMD and B)Non-TMD's global pain ratings (experimental and clinical pain if any) for up to two hours after capsaicin or vehicle cream application. Application of capsaicin increased reported pain as compared to vehicle in both healthy and TMD symptomatic subjects. There was a significant increase in VAS ratings over time for the capsaicin treated group as compared to vehicle treated subjects (ANOVA, $P < 0.001$).

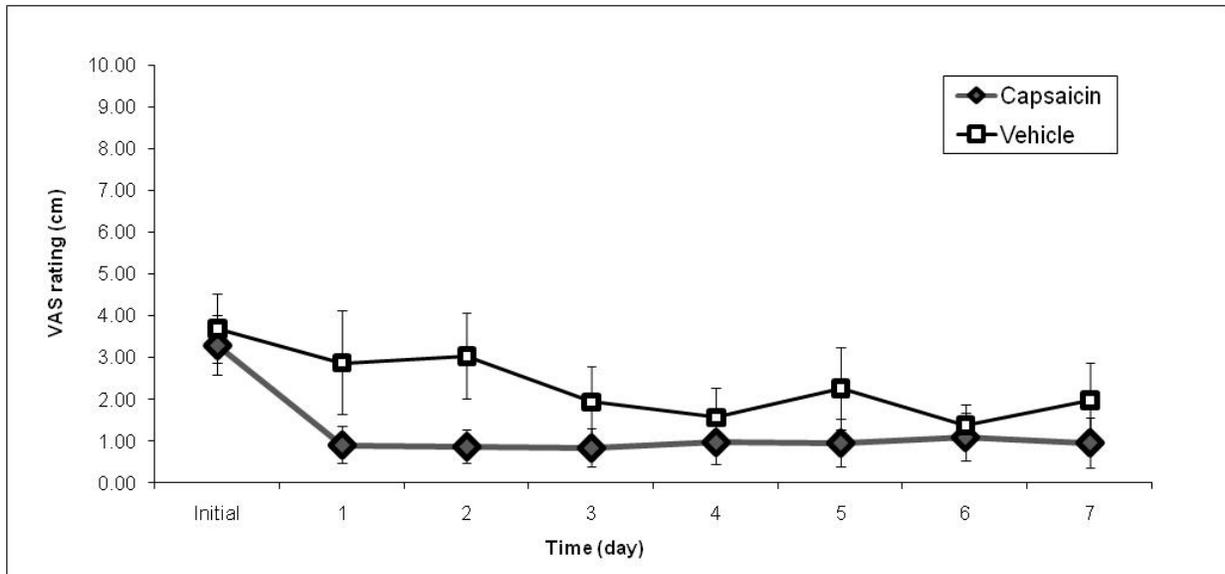
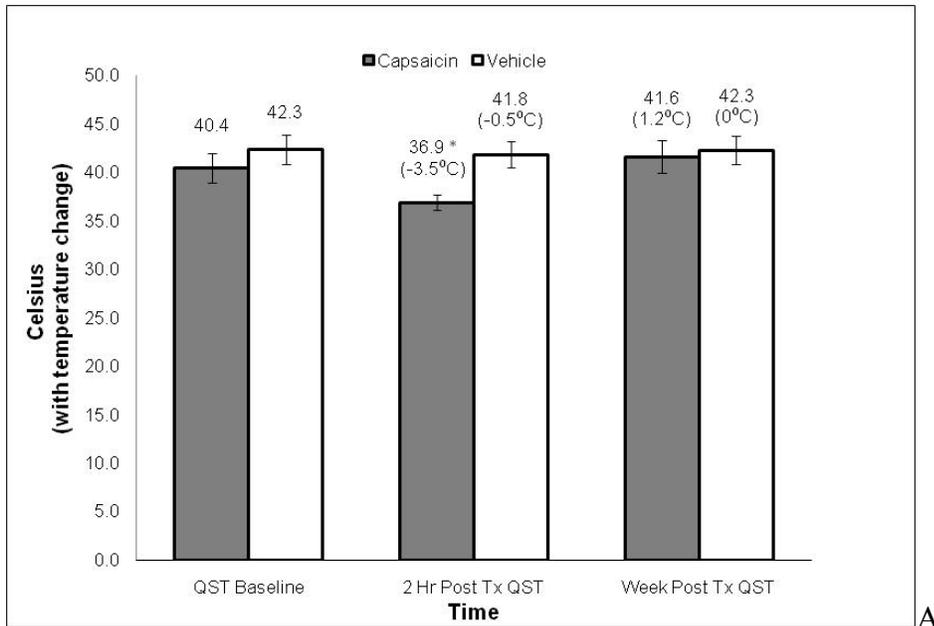
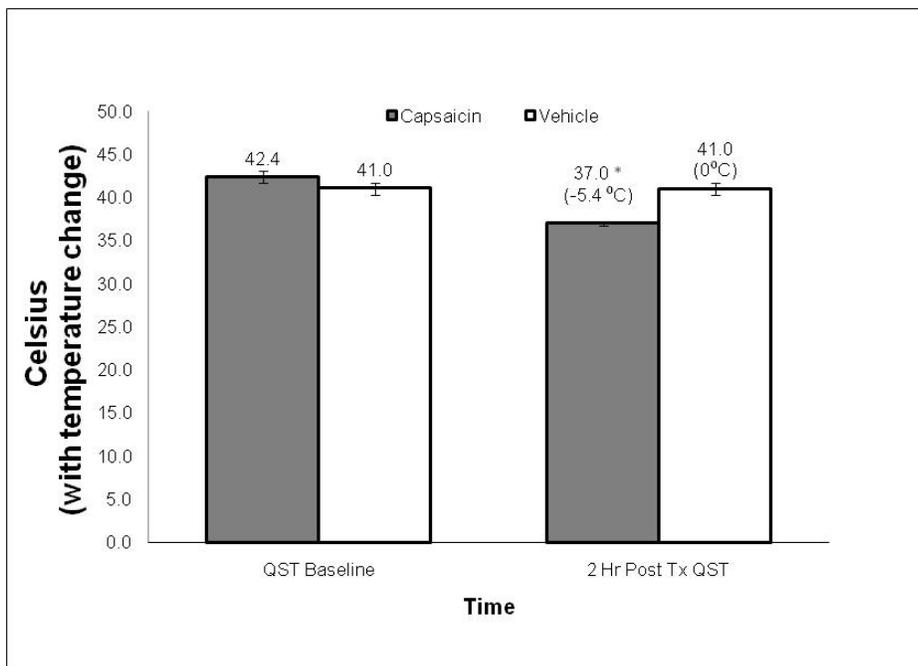


Figure 3-2. TMD groups' global (TMD) pain rating at initial time point (prior to any QST) and seven days post-treatment. The VAS measures during 5 to 120 min were significantly lower in the control vehicle group than in the capsaicin treatment group ($P = 0.002$). The VAS measures during 5 to 120 min were decreased over time ($P < 0.001$). The VAS measures during 1 to 7 days were significantly greater in the control vehicle group than in the capsaicin treatment group ($P = 0.001$). The VAS measures during 1 to 7 days showed an unknown tendency over time due to inadequate sample size ($P < 0.001$). The pattern of VAS measures was reversed in case of capsaicin treatment in the long run ($P = 0.033$).



A



B

Figure 3-3. Effects of capsaicin on thermal pain threshold within subject comparison. A) TMD (n=8) and B) non-TMD (n=30) capsaicin groups demonstrated a significant decrease in thermal pain threshold (-3.5°C and -5.4°C respectively) (Paired T test $p < 0.05$) at two hours post cream application. No change was observed one week later A) TMD and C) non-TMD (n=10). No change of thermal pain threshold was observed at any time in the vehicle.

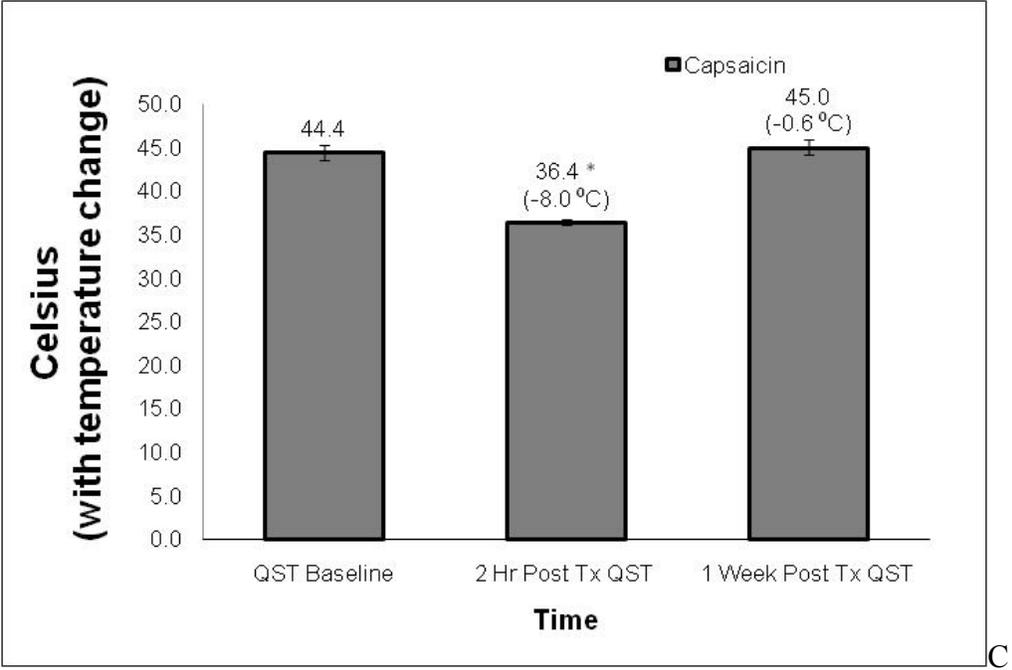


Figure 3-3. Effects of capsaicin on thermal pain threshold within subject comparison.

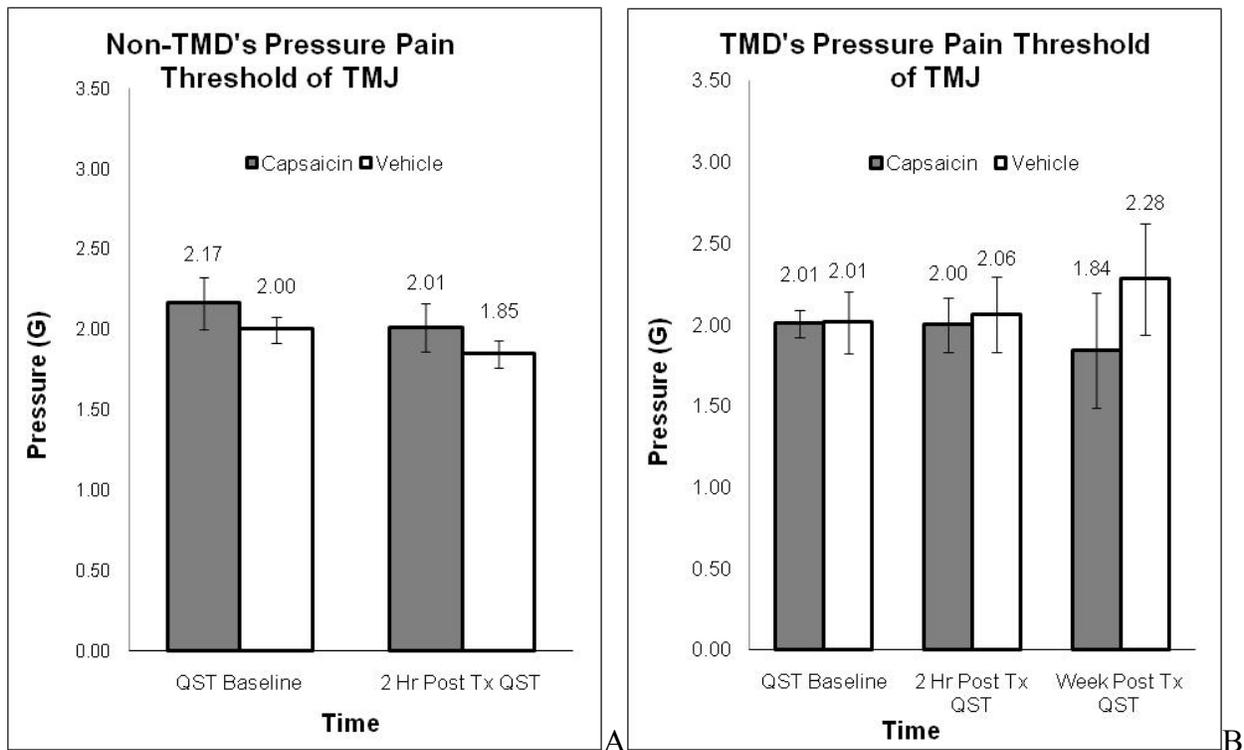


Figure 3-4. Pressure pain threshold changes. A) Non-TMD's and B) TMD's Pressure pain threshold changes following capsaicin or vehicle application. TMJ pressure pain threshold was not significantly changed following either capsaicin or vehicle treatment, as compared to baseline levels nor between respective groups within the non-TMD or TMD subjects.

CHAPTER 4 DISCUSSION

Less TMD pain was reported in the week following capsaicin as compared to the vehicle. Capsaicin decreased thermal pain threshold two hours after application but not one week later it did not affect pressure pain threshold across time. All groups were similar in age and ethnicity. Each finding will be discussed below.

Figure 3-2 suggests that capsaicin may have some clinical benefits of relieving TMD pain disagreeing with a previous capsaicin TMD study that found no difference between the TMD and healthy control groups [21]. This discrepancy could be attributed to their use of low dose capsaicin to our high dose and that they collected their reported pain weekly whereas our study collected it daily. Therefore their interval in reporting pain may be too far apart. The data showed a difference between the TMD capsaicin and vehicle groups as a whole over the entire seven days post cream application but due to limited recruitment of subjects tendency over the week is unknown.

It is not too surprising that during the two hours after capsaicin application that both TMD and healthy subjects found it to be a painful experience that lasted for some time. An hour after capsaicin application the TMD group pain returned to or was below initial pain levels. The TMD group receiving vehicle had no increase in pain but was level and dropped off towards the end. As noted 2 of 38 individuals felt like the pain was too much and did not want to continue suggesting that some of the population may have poor compliance with the present treatment modality.

The thermal threshold results showed that regardless of disease state of the group (TMD vs. non-TMD), the threshold decreased only on the side ipsilateral to the capsaicin and was only

seen at the two hour time point rather than seven days out. At first glance this finding seemingly contradicts previous findings of desensitization one week later after a two hour application of 8% capsaicin or three weeks later after multiple daily low dose capsaicin applications at the same skin site [14; 15]. The difference in the findings is thermal sensitization determines when a subject first feels warmth (sensitization) rather than pain due to heat (thermal pain threshold) and both studies were not testing facial skin which may react differently than the arm or inner thigh.

The decreased TMD pain over the course of the week is seemingly incongruent with the thermal pain threshold that did not maintain a decrease one week out compared to baseline. These findings may be explained by the placebo effect. Although the patients were told that they may or may not get capsaicin, the burning sensation likely made treatment assignment readily apparent to the women. They then might expect some relief. Alternatively, it is known that capsaicin can deplete neuropeptides like substance P which has no relationship to thermal pain and therefore may decrease associated symptoms to inflammation around the TMJ.

Lastly, the pressure pain threshold, no matter what grouping or comparisons to other groupings demonstrates that capsaicin has no effect in changing the threshold both at two hours or one week after application and regardless the site tested (i.e. the masseter or TMJ). These findings argue that the peripheral and central effects of topical capsaicin do not influence perception of mechanical pressure pain. This finding is in contrast to findings regarding mechanical allodynia induced by topically applied 0.075% capsaicin [26]. However, that mechanical stimulus involved application of a moving light touch using a paint brush, which differs substantially from the pressure pain stimulus used in the current protocol.

Limitations of this study include the relatively low “n” value for the TMD groups and so all conclusions are tentative and require further evaluation in a larger study. The study could be improved by including a seven day diary assessing the daily level of pain prior to the initial visit so as to have a better baseline rather than a single time point to compare a whole week’s worth of global pain. Any experience with TMD patients suggests that the perceived pain is highly variable. Therefore it could be argued that in recruiting patients for our study we biased the study by recruiting patients that do not necessarily experience the stated pain that they came in with on a normal basis. Alternatively, including patients that would be recruited in a similar manner that would not undergo any QST testing or capsaicin application, would be given a seven day diary could also help tease out any bias.

CHAPTER 5 CONCLUSIONS

Our experimental approach utilized established quantitative sensory testing techniques in order to evaluate the effects of 8% capsaicin cream compared to placebo control cream in TMD and non TMD subjects. Capsaicin had no effect on pressure (mechanical) pain threshold in both TMD and healthy individuals. Those subjects receiving capsaicin became sensitized to heat regardless if part of the TMD group or not. A trend for lowering pain in TMD capsaicin group suggests a possible therapy but more subjects are needed to evaluate this relationship thoroughly.

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BIOGRAPHICAL SKETCH

Benjamin K. Campbell was born of goodly parents residing in Willard, Utah. He was active in his youth church program and scouting, earning the Eagle Scout Award. After graduating Box Elder High School, he served a Spanish-speaking proselyting mission for the Church of Jesus Christ of Latter Day Saints for two years at his own expense in the foreign land of Idaho. In the summer of 1997, after the completion of his mission, he studied at Weber State University majoring in chemistry, minoring in Spanish, and was awarded a Bachelor of Science degree in 2000. He took a year off from school, entering the workforce as a chemist and had a wonderful time working for Thatcher Chemical and Albion Laboratory. In March of 2003 he married a lovely and beautiful lady, Dana, and they had their first child, Grace, in May of 2004. After completing dental school, he was awarded his Doctor of Dental Surgery degree in 2005. Upon completion of a one-year fellowship in orthodontics at the University of Florida, he entered their orthodontic program graduating in May 2009. He and his wife had two more children during his residency, Sadie (July 2006) and Hayden (April 2008), and, yes, they plan to have more! He tries to live up to a quoted principle, “No success outside of the home will compensate for failure in the home,” when balancing life’s priorities—family, work, and play