Topical Application of Capsaicin for the Treatment of Localized Pain in the Temporomandibular Joint Area

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Aims: *To determine the effectiveness of topical capsaicin cream application on localized pain in the temporomandibular joint (TMJ) area.* **Methods:** *A randomized, double-blind, placebo-controlled study was conducted on 30 patients suffering from unilateral pain in the TMJ area. Patients were randomly divided into experimental and placebo groups; they were instructed to apply 0.025% capsaicin cream or its vehicle to the painful TMJ area 4 times daily for 4 weeks. Subjective parameters of present pain, most severe pain, effect of pain on daily activities, and pain relief were assessed each week on a visual analog scale. Muscle and joint sensitivity to palpation on the painful and contralateral joints and maximal mouth opening (assisted/passive and non-assisted/active) were examined weekly by the same experienced examiner.* **Results:** *Capsaicin cream produced no statistically significant influence on measured variables when compared to placebo. Both experimental and placebo groups showed statistically significant improvement in most variables during the experiment.* **Conclusion:** *The factor of time had a major effect in the non-specific improvement of the parameters assessed. The placebo effect played an important role in the treatment of patients with pain in the TMJ area.*
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Key words: capsaicin, temporomandibular joint, placebo effect, temporomandibular disorders

Capsaicin is a topical analgesic currently approved by the United States Food and Drug Administration for pain relief.[1] It causes the release of substance P and pain-related neuropeptides and can be considered as an agent with both antinociceptive and anti-inflammatory properties.[2] It has been used for rheumatoid arthritis,[3] osteoarthritis,[3–6] neck pain,[7] atypical odontalgia,[8] post-mastectomy pain,[9] painful diabetic neuropathy,[10] and various neuralgias.[11,12]

Nerve fibers containing substance P have been found in the capsule of the temporomandibular joint (TMJ), disc attachment, fascia, and periosteum, and in the interfascicular connective tissue of the lateral pterygoid muscle in monkeys.[13] Since substance P and prostaglandin E_2 are elevated in the TMJ synovial fluid in inflammatory conditions,[14,15] topical application of capsaicin may be effective in these cases.[1]

In commercial preparations, the concentration of capsaicin ranges from 0.025% (equivalent to 0.8 mmol/L) to 0.075% (equivalent to 2.5 mmol/L). Its analgesic effect generally begins after 14 days of use but can occur within a few days.[16,17] Side effects include heat sensation and local burning on the topical area

of application, with possible local redness. With time, side effects diminish and slowly disappear.[16,18]

The purpose of this study was to determine the effectiveness of topical capsaicin cream application on localized pain in the TMJ area.

Materials and Methods

Study Population

From a large sample of patients referred to the Clinic for Craniomandibular Disorders at the School of Dental Medicine, Tel Aviv University, 30 patients who suffered from localized unilateral pain in the TMJ area were consecutively selected to participate in the study according to criteria specified below. The clinical protocol was approved by the Committee for Approval of Human Study Experiments of the Sackler Faculty of Medicine, Tel Aviv University.

Inclusion Criteria. All the following needed to be present:

1. History of TMJ pain for at least 3 months in a well-localized area
2. Pain in the joint area associated with function
3. Presence of TMJ tenderness to palpation on the reported side
4. An informed consent and agreement to participate in the study

None of the following anamnestic criteria were present:

1. Presence of general neurologic disturbances (sensory or reflex changes, weakness, etc) according to the medical history
2. Uncontrolled hormonal disease (diabetes, thyroid or parathyroid disease, etc)
3. Presence of neoplasm
4. Known psychiatric problems

Patients were randomly divided into 2 groups. The experimental group (Cap) consisted of 17 patients (14 females, mean age 35.6 ± 14.2), who received treatment with an active capsaicin cream as described below. The placebo group (Pla) consisted of 13 patients (10 females, mean age 37.5 ±16.7), who received treatment with a non-active vehicle.

Clinical Evaluation of Patients

Each patient underwent a comprehensive craniomandibular examination, including dental and medical histories. Information regarding pain behavior and side effects of cream application was gathered each week during the experiment as follows:

1. Severity of present pain at day of examination on a visual analog scale (VAS), referred to as "present pain" (PresP).
2. Worst pain experienced during the last week on VAS, referred to as "maximal pain" (MaxP).
3. Degree to which pain caused a change in the daily work and social and family activities on VAS, referred to as "daily activities" (DA).
4. Improvement level in pain intensity evaluated during the past week on VAS (ranging from 0 = no pain relief to 10 = complete relief). The variable was marked as "pain relief scale" (PRS) and was collected at the end of each consecutive week of the experiment.
5. Intensity of local warmth and burning sensations due to cream application on a scale from 0 to 4.

The questionnaire was answered and placed in a closed envelope by the patient to maintain the double-blind experiment.

All patients were examined by 1 experienced clinician, whose hand pressure was calibrated by numerous trials on scales and successfully tested for intraexaminer reliability prior to each patient examination. The following variables were examined:

1. Sensitivity to manual palpation of the superficial masticatory muscles (origin and insertion of the masseter and anterior and middle portion of the temporalis) on the painful joint side and on the contralateral side. Approximately 2 lbs of pressure were exerted.[19] Results were estimated as no, mild, moderate, or severe pain (0 to 3 points, respectively) and were calculated as an arithmetic average for the muscle sites on each side separately. Muscle sensitivity on the painful ipsilateral joint was marked as MSI and on the contralateral non-painful joint as MSC.
2. Sensitivity to palpation of the lateral pole of the joint on the painful and non-painful sides, at a pressure of about 1 lb (present or absent). Variables were marked as painful joint (PJ) and non-painful joint (NPJ).
3. Range of mouth opening in millimeters. The intrinsic distance was measured in active (voluntary) maximal mouth opening (AMO) and in passive (assisted) maximal opening (PMO) by applying finger pressure to extend the opening to its maximal capacity.

Table 1 Clinical Evaluation of the Examined Parameters at Start (T-0) and at End (T-4) of the Experiment

Signs and symptoms	T-0		T-4	
	Capsaicin	Placebo	Capsaicin	Placebo
PresP (VAS, 0 to 10)	7.25 (1.00)	6.65 (2.32)	3.39 (2.62)	4.00 (2.50)
MaxP (VAS, 0 to 10)	8.18 (1.10)	7.85 (1.57)	4.82 (2.97)	5.73 (2.55)
DA (VAS, 0 to 10)	2.18 (2.37)	3.34 (3.12)	2.11 (2.49)	3.23 (2.97)
AMO (mm)	38.2 (8.1)	43.2 (8.4)	39.2 (8.5)	46.2 (10.4)
PMO (mm)	39.9 (8.8)	45.4 (7.8)	41.9 (8.7)	45.5 (10.1)
MSI (range 0 to 3)	0.39 (0.49)	0.44 (0.57)	0.07 (0.21)	0.25 (0.42)
MSC (range 0 to 3)	0.11 (0.19)	0.13 (0.28)	0.04 (0.09)	0.11 (0.24)
PJ (no.)	15	13	11	10
PRS	—	—	4.3 (3.2)	4.5 (2.6)

Mean and SD for variables concerning the following parameters at start and at week 4 of experiment. PresP = present pain; MaxP = maximal pain; DA = effect of pain on daily work and social and family activities; AMO = active mouth opening; PMO = passive mouth opening; MSI = muscle tenderness to palpation at side of painful joint; MSC = muscle tenderness to palpation at side of contralateral joint; PJ = number of joints with sensitivity to palpation on the painful side; PRS = pain relief scale.

Procedure

Two sets of medicated cream tubes were prepared, one containing 0.025% capsaicin cream (Zostrix, RAFA Laboratories Ltd), the other without the active component (capsaicin). All tubes were prepared by RAFA Laboratories and appeared completely identical.

The study was conducted in a randomized, double-blind fashion. Neither the patient nor the examiner was aware of the tube contents. Patients were informed of the possibility of receiving either a capsaicin or placebo tube, and that both creams might or might not cause a warm, stinging or burning sensation when applied to the area. Instructions were to apply a small amount of cream (approximately the size of a pea) to the painful area and to gently rub it into the skin for 20 to 30 seconds until completely absorbed. This procedure was to be repeated 4 times daily. Patients were to wear a glove and to avoid proximity to the eyes.

All clinical and anamnestic variables except PRS were evaluated 5 times as follows:

- Time 0 (T-0): baseline data collection and start of cream application
- Time 1 (T-1): after 1 week of cream application
- Time 2 (T-2): after 2 weeks of cream application
- Time 3 (T-3): after 3 weeks of cream application
- Time 4 (T-4): after 4 weeks of cream application

Statistical Analysis

To evaluate differences between treatment groups (Cap versus Pla) at baseline (T-0) regarding all collected clinical and self-report variables, *t* tests (for continuous variables) and Chi-square tests (for qualitative variables) were used. A 2-way analysis of variance (ANOVA) with repeated measures was used to analyze mean differences between groups (Cap versus Pla) and the effect of time (T-0, 1, 2, 3, 4) on *(1)* patients' subjective report (present pain, maximal pain, and effect of pain on daily activities); *(2)* subjective improvement of pain; *(3)* AMO; and *(4)* PMO. A 2-way ANOVA with repeated measures was used to analyze the effect of treatment (Cap, Pla); time (T-0, 1, 2, 3, 4); and location of pain (painful or non-painful side) on muscle sensitivity to palpation. A Chi-square test was used to evaluate differences between groups (Cap versus Pla) regarding joint sensitivity to palpation during 4 weeks of treatment. The level of significance was set at $P < 0.05$.

Results

Comparison Between Treatment Groups at Baseline

A comparison of treatment groups (Cap versus Pla) at baseline (T-0) for all collected clinical and self-report variables revealed no significant differences between groups (Table 1). The 2 variables

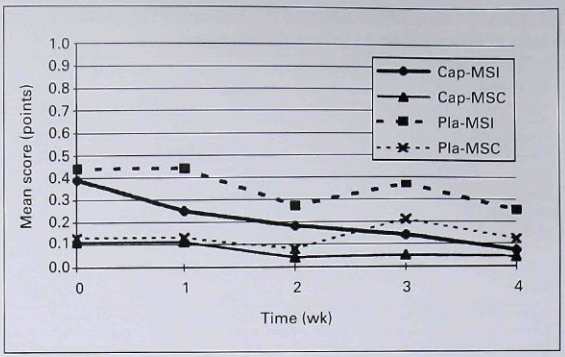

Fig 1 Muscle sensitivity to palpation during 4 weeks of treatment (expressed as a mean measurement on a scale from 0 to 3). Cap-MSI = capsaicin group, muscle sensitivity on the ipsilateral side; Cap-MSC = capsaicin group, muscle sensitivity on the contralateral side; Pla-MSI = placebo group, muscle sensitivity on the ipsilateral side; Pla-MSC = placebo group, muscle sensitivity on the contralateral side.

describing pain intensity showed relatively high scores for both groups. The mean present pain was 7.25 ± 1.00 for the Cap group and 6.65 ± 2.32 for the Pla group; mean maximal pain was 8.18 ±1.10 in the Cap group, versus 7.85 ± 1.57 in the Pla group. However, the degree of disturbances in daily social and family activity (DA) caused by the pain was rather low for both groups. The 2 variables expressing active and passive maximal mouth opening (AMO, PMO) showed a mild degree of limitation in both groups. No differences were found between groups in the pain level on either the painful or non-painful side regarding muscle and joint tenderness to palpation at baseline.

Effect of Treatment Mode on Patients' Subjective Report

Present Pain, Maximal Pain, and Effect of Pain on Daily Activities. Results showed no main effect of treatment (Cap versus Pla) concerning PresP, MaxP, and DA (Table 1). There was a significant main effect for time for PresP ($P = 0.0001$) and for MaxP ($P = 0.0001$) and no main effect of time for daily activities (DA). No interaction between treatment mode and time was found for these variables.

Pain Relief Scale. There was a significant main effect of time ($P = 0.0001$) but no main effect of the treatment group (Cap versus Pla) (Table 1). No interaction between the treatment group and time was evident, ie, the subjective improvement of pain (PRS) increased significantly during the experiment regardless of treatment.

Effect of Treatment Mode on Clinical Signs

Active and Passive Mouth Opening. No main effect of treatment (Cap versus Pla) was found on AMO and PMO (Table 1). A significant main effect for time was found for both AMO ($P = 0.0468$) and PMO ($P = 0.050$), with no interaction between treatment (Cap, Pla) and time.

Muscle Sensitivity to Palpation on the Painful and Non-Painful Sides. There was a significant main effect on the pain side ($P = 0.0012$) and of time ($P = 0.0018$) but no main effect of the treatment mode (Cap, Pla) on muscle sensitivity (Fig 1). A significant interaction was found between time (T-0, 1, 2, 3, 4) and the pain side ($P = 0.0206$). Muscle sensitivity on the painful joint side was significantly higher than on the contralateral side during the experiment. While MSI diminished with time in both treatment groups, MSC remained almost unchanged over time.

Joint Sensitivity to Palpation. Joint sensitivity to palpation on the painful side disappeared in only 4 of 15 patients in the Cap group and in 3 of 13 in the Pla group by the end of the experiment (Table 1). No significant differences were found between groups for this parameter.

Side Effects. As expected, side effects of capsaicin cream included a warm sensation, stinging, burning, or redness. Most of the Cap group (13 of 15 subjects) reported mild to moderate intensity at the beginning of the study (mean score of 1.7 ± 0.9). Two patients discontinued cream application on the first week because of an intolerable burning sensation and were excluded from statistical evaluations (total Cap group = 15). The incidence of side effects declined with consistent daily use, up to a mean of 0.3 ± 0.6 by week 4. Only 2 patients in the Pla group complained of a mild warm sensation and redness on the applied area.

Discussion

In this double-blind study, patients who had suffered from pain in the TMJ area for at least 3 months were evaluated over 4 weeks, and the effect of capsaicin as a treatment mode compared to a placebo was examined. The factor of time had a major impact on clinical findings and on patients' subjective reports of pain reduction. For most study parameters, patients benefited equally by the application of either capsaicin (0.025%) or a placebo cream. Previously, capsaicin was found to be effective in patients suffering from osteoarthritis and rheumatoid arthritis.[3–5,7] Schnitzer et al[6] found that capsaicin produced a significant decrease in articular tenderness in patients suffering from primary osteoarthritis of the hand compared to a placebo, but when the efficacy of the treatment measured as a reduction in pain intensity (on VAS) was compared to the placebo, there were no significant differences.

In the present study, both groups benefited from treatment over the 4-week period in a similar manner for most of the examined variables. The most pronounced improvement was expressed in the subjective criteria of the pain experience and pain relief reported by VAS (40% to 50% reduction).

Although significant improvement was also evident in the clinical signs, these findings were of limited clinical value. For example, the reduction in MSI was statistically significant for both groups. Since the initial basic levels of muscle sensitivity on both sides were rather low (less than 0.5 on a scale of 0 to 3; Fig 1), the clinical impact of this finding is almost negligible. Similarly, the statistical improvement in active and passive mouth opening and in joint sensitivity to palpation (for both groups) is of questionable importance (increase of 1.0 mm in active mouth opening in the Cap group and 3.0 mm in the Pla group; Table 1). It is our impression that the major clinical benefit of the applied treatment in both groups was the subjective feeling of patients regarding their individual pain experiences.

In a double-blind, placebo-controlled study, Deal et al[3] demonstrated the efficacy of topical capsaicin (0.025%) in 70 patients suffering from osteoarthritis and 31 from rheumatoid arthritis of the knee joint. Cream containing capsaicin or a placebo cream was applied 4 times daily for 4 weeks. Although pain reduction was significantly greater in patients who applied capsaicin than in those who applied placebo cream, a strong placebo effect was reported after the first and fourth week of treatment.

In the present study, patients were actively engaged in topical application of cream on the painful area 4 times daily. Their personal involvement in the treatment process, in addition to physician attention, interest and concern in a healing setting, patient expectations, etc, could have played a role in pain modulation and sensation that resulted in pain reduction. In other words, the lack of differences between the 2 treatment groups (Cap versus Pla) can be attributed to the placebo effect. The impact of the placebo effect is well documented in the medical and dental literature.[20,21] In 2 studies,[22,23] 100 temporomandibular disorder (TMD) patients were followed for 6 months to 8 years. Patients were managed with a diverse set of treatments (analgesics, tranquilizers, physical exercises, intraoral appliances, etc), along with various placebo treatments (inert drugs, non-occluding bite planes, mock equilibration, etc). There was marked improvement and only minor recurrences of symptoms in 92% of the patients. The common factors for the successful treatments were non-specific.

Another component involved in pain reduction could be the effect of the massage during the cream application.[24–26] Patients suffered from pain for at least 3 months before the experiment. The cyclic nature of TMD pain is well known[27]; however, it seems inconceivable that patients who continuously suffered from pain for 3 or more months would suddenly experience a significant recovery. In our opinion, the possibility of spontaneous recovery is less probable than the assumption that the non-specific placebo effects, rather than the specific active components (capsaicin 0.025%), played a role in the process of improvement.

Finally, it is conceivable that the lack of therapeutic effect of the 0.025% cream is at least partly due to the unique characteristics of TMJ anatomy and function. Further investigation is necessary before final conclusions can be reached.

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