Use of Theraflex-TMJ Topical Cream for the Treatment of Temporomandibular Joint and Muscle Pain

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ABSTRACT: This randomized, double-blind study was designed to evaluate the effectiveness of the topical cream Theraflex-TMJ (NaBob/Rx, San Mateo, CA) in patients with masseter muscle pain and temporomandibular joint (TMJ) pain. Fifty-two subjects (5 males and 47 females) were instructed to apply a cream over the afflicted masseter muscle(s) or over the jaw joint(s) twice daily for two weeks. Theraflex-TMJ cream was used by the experimental group, while a placebo cream was used by the control group. The means of pain ratings were calculated prior to the application of the cream (baseline), after ten days of tx (period 1), and 15 days of tx (period 2) days of treatment and five days after stopping the treatment (follow-up). There was a significant decrease in reported pain levels from baseline in the experimental group for period 1 ($p<0.01$), period 2 ($p<0.001$), and follow-up ($p<0.01$). For the control group, no significant differences were found between the different time periods ($p>0.05$). There was evidence of minor side effects such as skin irritation and/or burning on the site of the application in two subjects in the experimental as well as two subjects in the control groups. The data strongly suggest that Theraflex-TMJ topical cream is safe and effective for reducing pain in the masseter muscle and the temporomandibular joint.

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Myofascial pain and temporomandibular joint pain cannot be fully understood without an appreciation of the evolution in our understanding of the pathophysiology of chronic musculoskeletal pain and joint pain syndromes. The earliest reports on muscle pain were catalogued by Simons,[1] first appearing in the German medical literature in the 19th century. These early reports contain a host of symptoms characterized by chronic pain of unidentifiable cause. Some patients had localized pain while others had a generalized pain syndrome. Simons described the characteristic physical findings of these conditions and found that a common feature was "an easily identifiable muscle hardness known as *Muskelshwiele*" (muscle callus), which was tender to palpation and hence thought to be responsible for the patient's clinical complaints.

Dolwick, et al.[2] suggested that "by the 1950s it was becoming obvious that many of these patients suffered from a masticatory muscle disorder apparently unrelated to the temporomandibular joint (TMJ)." With the aid of modern TMJ imaging techniques, it became clear that there were also temporomandibular disorders (TMD) of

the joint proper that justified separate classification, a separate entity of temporomandibular joint pain (intracapsular) as opposed to the *general* myofascial pain dysfunction syndrome. This differentiation is evident in the most used guidelines for diagnosis of temporomandibular disorders.[3,4]

Treatment of TMJ and muscle pain has included patient education and self-care, cognitive behavioral intervention, pharmacologic management, physical therapy, occlusal splint therapy, and surgery.[5-10]

Pharmacotherapy has been useful as a first step in the treatment of myalgia and arthralgia. The most common medications include analgesics (i.e., aspirin and opioids); and nonsteroidal anti-inflammatory drugs (i.e., ibuprophen, naproxen fenoprophen, indomethacin, corticosteroids, anxiolytics, muscle relaxants, and tricyclic antidepressants).[4] Other forms of pharmacotherapy including topical analgesics work as counter-irritants.

One preparation, Theraflex (Nabob/Rx, San Mateo, CA), was originally designed and used to treat muscle sprains and ostearthritis in adults. More recently, a product with less potency, Theraflex-TMJ (NaBob/Rx, San Mateo, CA), was formulated to treat the signs and symptoms of TMJ disorders.

The required counter-irritant ingredient is methyl salicylate (oil of wintergreen) present in a concentration accepted for general use.

Theraflex-TMJ also contains copper pyrocarboxylate and zinc pyrocarboxylate because of the key role that copper and zinc have in controlling inflammation. Additionally, the pyrocarboxylate amino acid component renders ions and trace elements included in the preparation remarkably soluble with enhanced skin and tissue penetrability.[11,12]

Molecular genetic research and several clinical discoveries during the past 20 years have produced major advances in our understanding of copper's role in physiology. We now better understand the role of copper in energy production in the body, metabolism of oxygen, metabolism of iron, and the maturation of the extracellular matrix and neuropeptides.[13]

For 1,000 years copper has been believed to be of therapeutic value. Copper bracelets have been found on Egyptian mummies with evidence of arthritic conditions. The validity of folkloristic use of copper bracelets has now actually been sustained scientifically. Walker, et al.[14] took up the challenge of the copper bracelet *myth* and showed that, indeed, significant amounts of copper were absorbed from the bracelets, to the extent of 13 milligrams per month. Dissolved copper penetrated the skin, and, in a single blind crossover study, copper bracelets were shown to be effective at reducing the pain of rheumatoid arthritis. Regular bracelet wearers differentiated between copper bracelets and placebo (anodized aluminum) bracelets and reported significantly worse symptomatology when not wearing the copper bracelets.

This modulator effect of copper in arthritic pain has been supported by Milanino, et al.[15,16] where they demonstrated that a copper supplemented diet has an anti-arthritic effect in rats. Sorenson[12] reported that anti-arthritis agents promoted the tissue distribution of physiologically elevated serum copper in patients with rheumatoid arthritis.

Conforti, et al.[17] studied patients with rheumatoid arthritis. They found that patients had significantly elevated serum copper and ceruloplasmin concentration compared to the normal subjects group and the degenerative joint disease group. This supports the hypothesis by Rainsford[11] that deficiency or impairment of copper absorption by the cells could be a relevant factor in the etiology of rheumatoid arthritis.

According to Milanino,[18] copper is stored in the liver until required systemically to respond to inflammatory stress. It is then released by the liver in the form of copper-amino acid or copper-protein (ceruloplasmin) complexes and delivered to sites of apoenzymes, converting these to the active enzymatic forms, superoxidase dismutase (SOD) and lysyl oxidase (LO). SOD is the key anti-inflammatory enzyme in the body. SOD functions in controlling or turning-off inflammation by scavenging and inactivating the highly reactive and tissue-damaging free radicals, superoxide and hydroxyl radical, generated during the inflammatory response. Inadequate delivery of copper to an inflammatory site results in tissue damage, and increased delivery of copper, either physiologically or exogenously, enhances the enzymatic control of inflammation (pain, swelling, redness) and reduces tissue damage.[15,19,20] According to Berthon,[21] prevention of hydroxyl radical damage in inflamed tissues would simultaneously require sufficiently high levels of copper and copper specific hydroxyl inactivating ligands at the site of inflammation.

Copper is also the key ligand required for activation and function of tissue LO. LO plays the key role in cross-linking and stabilizing collagen and elastin, essential structural components of the connective tissue of joints and supporting structures. Deficiencies of copper dependent LO result in slow or inadequate healing after inflammation or injury, and account for vascular abnormalities. On the other hand, high levels of LO promote fast and effective healing and might offer an additional safeguard against oxidative stress.[22,23]

Failla[24] proposed that the anti-inflammatory action of copper includes the direct inhibitory effect of prostaglandin

synthesis, the byproduct of which is the production of free radicals. In addition, copper is known to stabilize lysosomal membranes in phagocytes, preventing the release of lysosomal enzymes that contribute to the tissue damage in inflammation.

Thus, the role of copper in preventing or reducing tissue damage is due to three main actions: direct reduction of the generation of free radicals, inactivation of damaging free radicals generated during the inflammatory process, and prevention of the release of tissue-damaging lysosomal enzymes.[25]

On the other hand, the history of recognition of the role of zinc in biology is relatively brief. In 1934 zinc was shown to be an essential nutrient for rats, by 1958 it was recognized as necessary for humans, but it was only in the early 1960s that it was recognized as a common deficiency in human populations.[26]

Zinc is present in virtually all cells, but the concentration varies among tissues in a pattern that is similar across animal species. The high zinc content of specific organs and compartments is derived from intracellular sites of high zinc-binding affinity, also related to influx-efflux transport systems. The highest concentrations are found in bone and prostate. In most soft tissue (e.g. muscle, brain, lung) zinc concentrations are relatively stable and unresponsive to dietary zinc intake over most normal ranges of intake.[11,27,28]

Dibley[26] proposed that zinc plays an important role in human health because of its participation in multiple enzymatic reactions and its involvement in the immune system.

According to Fernandez-Madrid,[29] in the treatment for rheumatic disease, zinc deficiency profoundly disturbs the immune function and the host defense mechanism resulting in lymphoid atrophy, impaired delayed hypersensitivity, and T-helper cell dysfunction. Low serum zinc and high serum copper are characteristic of rheumatoid arthritis.

Another component of the cream is a soluble form of the dipeptide lysine-aspartic acid, which has been shown to be effective in reducing muscle spasm, enhancing muscle recovery, and acting as a general muscle stress reducer.[30] Finally, Theraflex-TMJ contains specific standardized 4:1 extracts of a combination of herbs selected for their known effects on tissue healing and restoration of normal tissue function. All these herbs are recognized as safe for external use by the American Botanical Council and by the authoritative German Commission E Monograph.[31]

The present research is designed to examine the efficacy of Theraflex-TMJ topical analgesic for the reduction of pain in the masseter muscle and TMJ.

Materials and Methods

Fifty-two subjects were solicited in order of appearance from patients seeking treatment at the Craniomandibular Pain Center at Tufts University, School of Dental Medicine. Five males and 47 females suffering from temporomandibular joint pain and masseter muscle pain volunteered.

The inclusion criteria were the following:

1. Report of pain in the masseter muscle either at rest or during function;
2. Pain on palpation of the masseter muscle;
3. Pain in the temporomandibular joint either at rest or during function; and
4. Good general health determined by a recent medical examination (within one year) and by a clinical questionnaire.

Selected subjects had pain in only one of the areas.

Exclusion criteria were:

1. Younger than 18 years old or older than 60 years old;
2. Face head and/or neck trauma within the past year;
3. Lesions in the oral cavity or deeper structures;
4. Systemic disease;
5. Pain or psychotropic medication use within a one month period;
6. Diagnosis of migraine; and
7. Pregnancy.

The study was conducted in a randomized double-blind fashion. Allocation to either the experimental or control group was accomplished by blind selection from a pool of 52 numbers (26 experimental and 26 control) in a box. Once the number was chosen, it was not returned to the box. A Gelb Center employee not on the research team performed selection. Numbers assigned to each subject were monitored by the employee and were not disclosed until the study was completed. Subjects were divided into two equal groups: experimental group, using Theraflex-TMJ cream (NaBob/Rx San Mateo, CA) and control group, using a placebo cream. Patients were instructed to apply 1/4 to 1/2 teaspoon of cream on the afflicted masseter muscle(s) or over the jaw joint(s) twice daily over a period of two weeks. The cream had to be rubbed on the skin until completely absorbed and left in place for seven minutes before washing it off.

All the subjects rated their pain level using a Numerical Graphic Rating Scale (NGRS). The NGRS is a ten point scale with verbal anchor at 0 (*no pain*), 5 (*moderate pain*) and 10 (*worst pain possible*).[32] Pain measures were at a spontaneous level and not elicited. The cream was applied twice a day, as soon as they woke up in the morning and before going to bed, for five days before starting the treatment, during the treatment, and for five days after

stopping the medication. The pain ratings mean was calculated prior to the application of the cream (baseline), after 10 (period 1), and 15 (period 2) days of treatment, and five days after stopping the treatment (follow-up).

The study was approved by the Human Investigation Research Committee at Tufts University Health Sciences. Informed consent was obtained from each subject, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Theraflex-TMJ

Theraflex is an over-the-counter (OTC) topical analgesic originally designed to treat muscle sprains and ostearthritis in adults. Later, Theraflex-TMJ (NaBob/Rx, San Mateo, CA), a product with less potency, was formulated to treat the signs and symptoms of TMJ disorders.

The purpose of the medication was to combine the pain relief of existing topical analgesics with anti-inflammatory effects. Theraflex complies with the FDA Monograph on Topical Anal-gesics. It is approved for use and commercial sale and is manufactured in an FDA approved laboratory. All ingredients are FDA and OTC approved for topical, cosmetic application.

Statistical analysis

To evaluate the baseline difference between the experimental group and the control group, a two-tailed independent t-test was conducted. A two factor AB mixed design ANOVA was performed to analyze pain levels at the different time periods. Subjects were divided equally: 26 for the experimental group and 26 for the control group. The pain levels in the experimental group and the control group were treated as the independent factor while time was used as a dependent factor. A two-way (AS) analysis of variance was performed to compare the means of the two conditions (masseter muscle pain and TMJ pain) in each independent factor over the study period. Subjects in the experimental group were divided into 14 for the TMJ group and 12 for the masseter group, as well as for the control group.The ANOVA was applied to the ratings on the Numerical Graphic Rating Scale. Two measurements on days 5, 10, 15, and 20 were averaged to yield a pain rating. The time periods were defined as baseline, period 1, period 2 and follow-up. Data are presented as mean and Standard Error of the Mean (±SEM).

Results

Pain rating scores using a Numerical Graphic Rating Scale (NGRS) were recorded as follows: baseline at day five, period 1 of treatment at day ten, period 2 of treatment at day 15 and posttreatment (follow-up) at day 20.

An independent Student's t-test showed that there was no statistical difference between groups at the beginning of the study in mean pain rating scores for both masseter muscle and TMJ pain (separately and combined), $p>0.05$.

Masseter Muscle and TMJ Pain

A two-way (mixed AB) factorial ANOVA was conducted to evaluate masseter muscle and TMJ pain levels over the four time periods. The analyses indicated a significant main effect in reduction of pain over the indicated times ($F_{df=3}=7.43$, $p<0.001$). Although there was no significant effect for groups ($F_{df=1}=3.38$, $p=0.10$), there was a significant group over time interaction ($F_{df=3}=2.44$, $p<0.05$).

Figure 1 shows that in the experimental group, pain levels decreased from baseline (mean=5.09) to period 1 (mean=2.55) and period 2 (mean=2.11), increasing at follow-up (mean=3.11). However, in the control group, pain levels from baseline (mean=4.25) to period 1 (mean=3.70) and period 2 (mean=3.66), and the mean at follow-up were essentially the same as in periods 1 and 2.

Post hoc multiple comparisons on all pairs of means showed that the mean reduction for the experimental group was significant from baseline to period 1 ($p = 0.01$) and from baseline to period 2 ($p = 0.001$), as well as from baseline to follow-up ($p = 0.01$). Conversely, no significant differences were found for the control group (**Table 1** and **Figure 1**).

TMJ Pain

A two way (AS) analysis of variance was conducted to evaluate TMJ pain levels in the experimental group. This analysis indicated that there was a significant effect between periods ($F_{df=3}=15.81$, $p=0.00001$).

Independent t-tests of all possible pairs for the experimental group showed that baseline compared to period 1, period 2, and follow-up showed a significant difference (respectively $t_{df=39}=5.47$, $p<0.001$; $t_{df=39}=6.28$, $p<0.001$; $t_{df=39}=3.23$, $p<0.01$), however, the mean pain in period 1 compared to period 2 and follow-up were not different (respectively $t_{df=39}=0.80$, $p>0.10$; $t_{df=39}=2.24$, $p<0.05$ >0.02) and period 2 compared to follow-up showed a significant difference ($t_{df=39}=3.05$, $p<0.01$). This most likely reflects an increase in pain after ceasing the application of the cream. No significant differences were found for the control group (**Figure 2**).

Masseter Muscle

A two-way (AS) analysis of variance was conducted to evaluate masseter muscle pain level in the experimental

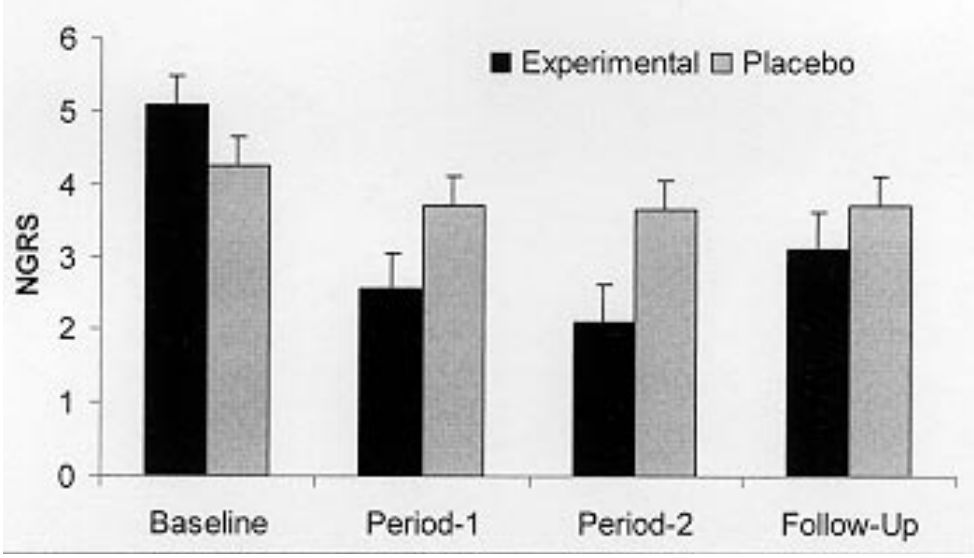

Figure 1
Mean pain levels and standard deviation for masseter muscle and TMJ in the experimental and control groups. At baseline, period 1, period 2, and follow-up. (n=52)

group. This analysis indicated significant effect for periods ($F_{df=3}$=10.7, p=0.00001).

Independent t test showed significance at baseline compared to period 1, period 2 and follow-up (respectively, $t_{df=33}$=4.35, $t_{df=33}$=5.19, and $t_{df=33}$= 4.09, p<0.001). However, the mean pain in period 1 compared to period 2 and follow-up were not different (respectively, $t_{df=33}$=0.84, $t_{df=33}$=0.25, $t_{df=33}$=1.10, p>0.10) (**Figure 3**).

A two-way (AS) analysis of variance was conducted to evaluate masseter muscle pain level in the control group. This analysis indicated no significant effect for periods ($F_{df=3}$=1.28, p=0.29).

Discussion

The use of topical analgesics have been shown to be effective in joint and muscle pain.[33,34] While creams and preparations have been used for many years, there has not yet been a preparation containing copper and zinc studied in human subjects.

The present data indicated significant beneficial results when Theraflex-TMJ was used for pain in the masseter muscle and temporomandibular joint. While both groups started out at almost equal pain levels, only the experimental group showed a significant decrease in pain level (59% from baseline) at the period 2 of treatment, and at the follow-up, pain level was still significantly less than baseline, but showed a decrease from baseline of 39%. This demonstrates that the pain level while using the Theraflex-TMJ reduced significantly and the results persisted even during the follow-up.

When the analysis was divided by condition, Theraflex-TMJ significantly reduced TMJ pain during period 2 by 50%, and after withdrawal of the medication, pain was still significantly less than baseline with a decrease of 26%. Theraflex-TMJ also significantly reduced pain in masseter muscles during period 2 (68%), and at follow-up (50%). This difference strongly suggests that Theraflex-TMJ has a greater effect on muscles than on the TMJ, but both conditions were responsive to the treatment. Moreover, masseter muscle pain showed a larger reduction than TMJ pain at follow-up (54% vs. 26%) showing a more prolonged effect (TMJ pain increased 24% from period 2 to the follow-up vs. 14% in the masseter group). There was also a decrease in pain in the control group, especially during the first period of treatment. This decrease, although not significant, can be due to the fact that the cream was rubbed on the muscle, and this action by itself has a relaxing effect on the muscle leading to reduction of pain.

The exact mechanism of action of Theraflex-TMJ is still unknown, but the effects of copper and zinc on inflammation and, consequently, pain may explain the beneficial effects of the cream.

Conclusions

Theraflex-TMJ has been shown to be a safe, non-invasive and effective treatment for reducing pain in masseter muscles and TMJs. It should be considered as part of the first line treatment or adjuvant therapy for the treatment of temporomandibular disorders.

Acknowledgements

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Table 1
Masseter and Temporomandibular Joint Pain
Two Factor (Mixed AB) Factorial ANOVA (N=52)

Source	DF	Sum of Squares	Mean Square	F-Ratio	P-Level
B/S	103	540.33374			
B	3	98.5417	32.8472	7.4346	0.0002
Error (B)	100	441.7957	4.4180		
W/S	104	6.46.2051			
A	1	19.7537	19.7537	3.3839	0.1056
AB	3	42.7014	14.2338	2.4383	0.0488
Error (W)	100	583.7500	5.8375		
Total	207	1186.5425			

Bartlett's Test for equality of cell variances B and AB each p>0.10 and A p<0.01

B Time

	Mean	SD	N
1 Baseline	4.6769	2.6680	52
2 Period 1	3.1308	2.3880	52
3 Period 2	2.8923	2.1434	52
4 Follow-up	3.4135	2.3571	52

1 vs 2<0.001
2 vs 3<0.001
1 vs 4<0.01 >0.001

A Condition

	Mean	SD	N
1 Theraflex	3.2202	2.6680	104
2 Placebo	3.8365	2.0518	104

BA Condition x time period

	Mean	SD	N	
1 Baseline	5.0962	2.4414	26	Theraflex
2 Baseline	4.2577	2.2033	26	Placebo
3 Period 1	2.5538	2.4024	26	Theraflex
4 Period 1	3.7077	2.2737	26	Placebo
5 Period 2	2.1154	2.1369	26	Theraflex
6 Period 2	3.6692	1.8842	26	Placebo
7 Follow-up	3.1154	2.7615	26	Theraflex
8 Follow-up	3.7115	1.8771	26	Placebo

1 vs 3 p<0.001
1 vs 4 p<0.05 >0.02
1 vs 5 p<0.001
1 vs 6 p<0.05 >0.02
1 vs 7 p<0.01 >0.001
2 vs 3 p<0.02 >0.01
2 vs 5 p<0.01 >0.001
4 vs 5 p<0.05 >0.02
5 vs 6 p<0.05 >0.02
5 vs 8 p<0.05 >0.02

"A" represents Condition; and "B" represents Time (baseline, period 1, period 2, and follow-up).

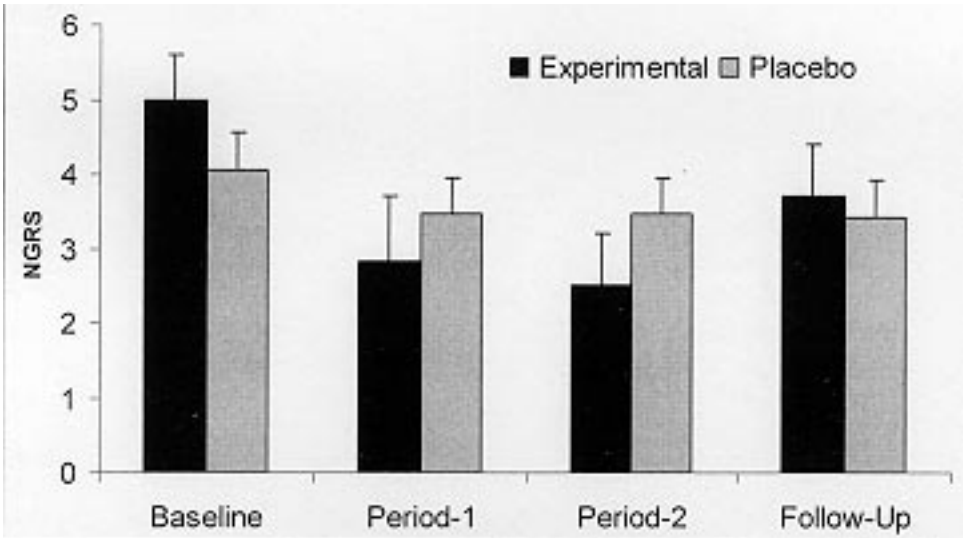

Figure 2
TMJ pain levels and standard deviation for masseter muscle and TMJ in the experimental and control groups. At baseline, period 1, period 2, and follow-up. (n=28)

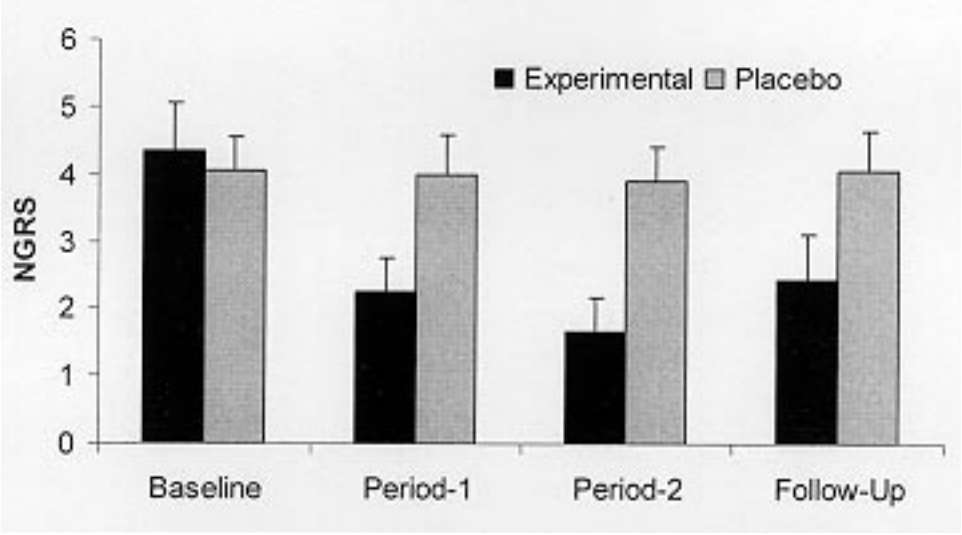

Figure 3
Masseter muscle pain levels and standard deviation for masseter muscle and TMJ in the experimental and control groups. At baseline, period 1, period 2, and follow-up. (n=24)

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