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.

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 Muskelschwiele” (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 (intra-
capsular) as opposed to the general myofascial pain dys-
function syndrome. This differentiation is evident in the
most used guidelines for diagnosis of temporomandibular
disorders.1,4

Treatment of TMJ and muscle pain has included patient
education and self-care, cognitive behavioral interven-
tion, 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., ibupro-
phen, naproxen fenoprophen, indomethacin, corticos-
teroids, 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 osteoarthritis in adults. More recently, a pro-
duct with less potency, Theraflex-TMJ (NaBob/Rx, San
Mateo, CA), was formulated to treat the signs and symp-
toms of TMJ disorders.

The required counter-irritant ingredient is methyl sali-
cylate (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 prepara-
tion remarkably soluble with enhanced skin and tissue
penetrability.11,12

Molecular genetic research and several clinical discov-
eries during the past 20 years have produced major
advances in our understanding of copper’s role in physi-
ology. 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 extracellu-
lar matrix and neuropeptides.13

For 1,000 years copper has been believed to be of ther-
apapeutic 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 mil-
ligrams per month. Dissolved copper penetrated the skin,
and, in a single blind crossover study, copper brace-
lets were shown to be effective at reducing the pain of
rheumatoid arthritis. Regular bracelet wearers differenti-
bated between copper bracelets and placebo (anodized alu-
minum) 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 demon-
strated that a copper supplemented diet has an anti-
arthritic effect in rats. Sorenson12 reported that anti-
arthritic agents promoted the tissue distribution of physi-
ologically elevated serum copper in patients with
rheumatoid arthritis.

Conforti, et al.17 studied patients with rheumatoid
arthritides. They found that patients had significantly ele-
vated serum copper and ceruloplasmin concentration
compared to the normal subjects group and the degenera-
tive joint disease group. This supports the hypothesis by
Rainsford11 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, convert-
ing these to the active enzymatic forms, superoxidase dis-
mutase (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 depen-
dent LO result in slow or inadequate healing after inflam-
mation 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

Failla24 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.36

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

Dibley26 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.20 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 Cranio-mandibular 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 osteoarthritis 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 Analgesics. 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(6,3) =7.43, p<0.001). Although there was no significant effect for groups (F(6,3) =3.38, p=0.10), there was a significant group over time interaction (F(6,3) = 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(6,3) =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(6,39)=5.47, p<0.001; t(6,39)=6.28, p<0.001; t(6,39)=3.23, p<0.01), however, the mean pain in period 1 compared to period 2 and follow-up were not different (respectively t(6,39)=0.80, p>0.10; t(6,39)=2.24, p<0.05 >0.02) and period 2 compared to follow-up showed a significant difference (t(6,39)=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
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. 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

This study was supported by NaBob/Rx (San Mateo, California).
### Table 1
Mastic and Temporomandibular Joint Pain
Two Factor (Mixed AB) Factorial ANOVA (N=52)

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<th>F-Ratio</th>
<th>P-Level</th>
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<td>B</td>
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<td>19.7537</td>
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Bartlett’s Test for equality of cell variances B and AB each p>0.10 and A p<0.01

#### B Time

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<td>Follow-up</td>
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1 vs 2 < 0.001
2 vs 3 < 0.001
1 vs 4 > 0.01

#### A Condition

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#### BA Condition x time period

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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

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


Dr. Noshir R. Mehta is Professor and Chairman of General Dentistry and Director of the Craniofacial Pain Center at Tufts University School of Dental Medicine, Boston, Massachusetts. He holds a Diplomate from the American Board of Orofacial Pain and is a Fellow of the International College of Dentists. Since receiving his D.M.D. degree and his M.S. in Periodontics at Tufts University, he has been involved in occlusion research. Dr. Mehta has lectured internationally on TMD/MPD and has published numerous scientific papers.

Dr. Albert Forgione is the Chief Consultant of Craniofacial Pain Center at Tufts University School of Dental Medicine, Boston, Massachusetts. He received a Ph.D. in psychology from Boston University and then joined Tufts University and lectured in Behavioral Medicine. Dr. Forgione established the TMJ center at Tufts University School of Dental Medicine with Dr. Mehta in 1978.

Dr. Marcello Melis received his degree in Pharmacy from the University of Cagliari (Italy) in 1990, and his D.M.D. from the Dental School of the same university in 1998. He was a resident in the Gelb Orofacial Pain Center at Tufts University, Boston (U.S.A.) from 1998 to 2000. Currently he practices in Cagliari in the field of TMD and orofacial pain, and he has been involved in several international research activities focusing on TMD and orofacial pain, occlusion, and muscle function.

Dr. Emad A. Al-Badawi received his B.D.S. degree at the King Abdulaziz University Faculty of Dentistry in Jeddah, Saudi Arabia in 1995. He spent the next three years as an oral surgery resident at King Fahad Hospital, Jeddah, Saudi Arabia. In 1998 he joined the TMD and Orofacial Pain Program at the Craniofacial Pain Center at Tufts University School of Dental Medicine, Boston, Massachusetts and was awarded an M.S. degree in 2001. Currently, Dr. Al-Badawi is a senior resident at the Pediatric Dentistry Department at Tufts University School of Dental Medicine.

Dr. Fahad Zawawi received his B.D.S. at Punjab University, De’Montmorency College of Dentistry, Pakistan in 1992. He spent six years as a clinical specialist in the Department of Oral Surgery at King Abdulaziz University, Faculty of Dentistry in Jeddah, Saudi Arabia. In 2001, he completed the certification program in TMD and orofacial pain at the Craniofacial Pain Center at Tufts University School of Dental Medicine, Boston, Massachusetts. Dr. Zawawi is currently at research associate at the Gelb Center and is working on a Doctor of Science degree in oral biology at the Boston University School of Dental Medicine.

Dr. Caroline Ceneviz received her dental degree from UNIARARAS in Sao Paulo, Brazil in 2001. She completed her fellowship in TMD and orofacial pain in 2003 at Tufts University School of Dental Medicine, Boston, Massachusetts. She is currently pursuing her Master’s degree at the same institution.