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TOPICAL ANALGESIA

The effect of cetylated fatty esters and physical therapy on myofascial pain syndrome of the neck

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Summary Participants with Myofascial Pain Syndrome (MPS) of the neck were randomly assigned into 2 groups of the double-blinded study: topical cetylated fatty ester complex (CFEC) cream application plus physical therapy (CF-PT; $n = 37$), and placebo cream application plus physical therapy (PL-PT; $n = 35$). There were 3 visits during 4 weeks of treatment. Physical Therapy (PT), given twice/week, included Ischaemic Compression, Deep Pressure Trigger Point Massage and Myofascial Releases. Topical cream [CFEC cream (5.6%) and 1.5% menthol] or placebo cream [1.5% menthol, in a cream base] was applied twice/day. CF-PT provided the fastest and most effective study treatment modality. The addition of CFEC cream to PT resulted in statistically significant improvements, compared to PL-PT, for reduction of pain, neck disability and life quality indicators. Our results indicate that cetylated derivatives of fatty acids can effectively reduce pain and symptoms associated with neck MPS, when combined with physical therapy.

Introduction

Myofascial Pain Syndrome (MPS) is one of the most common, non-articular forms of musculoskeletal pain (Fricton, 1989; Shah et al., 2008). In a chronic pain centre 85% of 283 consecutive patients received a primary diagnosis of MPS (Fishbain et al., 1986). MPS is associated with ''hyperirritable spots'' or ''trigger points'' (MTrPs) within palpable taut bands

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of skeletal muscle or fascia that are painful on compression. These can give rise to characteristic referred pain, tenderness, and autonomic nervous system symptoms (Simons 1995; Simons et al., 1999). Muscles with active MTrPs are more tender and mechanically sensitive than normal muscle, which do not contain MTrPs (Shah and Gilliams, 2008; Simons et al., 1999). Furthermore, MTrPs in the trapezius has been proposed as the main cause of temporal headache (Wolfe et al., 1992), cervicogenic headaches, and neck pain (Simons, 1995; Grosshandler et al.,1985; Gerwin et al., 2004).

Of numerous treatment approaches, physical therapy (PT), including Ischaemic Compression and Myofascial Release, currently provides the most promise and symptomatic improvement (Simons et al., 1999; Hou et al., 2002). MTrP Injections (with or without local anaesthetics), spray and stretch and TENS have all shown benefit, while less stimulatory interventions, such as laser and ultrasound, have not convincingly been shown to be beneficial (Huguenin, 2004). Other treatments include osteopathy, yoga, acupuncture, EMG biofeedback and cognitive behavioural therapy (Hong, 2002; Maigne, 1996; Frobb, 2003). Many treatments in widespread use are poorly validated and not necessarily more effective than placebo (Huguenin, 2004).

Pharmacological treatment includes nonsteroidal anti-inflammatory agents (NSAIDs), steroids, analgesics, and antidepressants (Simons et al., 1999) but significant side effects raise concern about long term use. Botulinum Toxin injection to the MTrPs has been used to reduce muscle activity. An early pilot trial showed a modest pain reduction (Cheshire et al., 1994), but a subsequent trial found no significant therapeutic efficacy (Qerama et al., 1996), while another study found that 17% had moderate to severe side effects, which included impaired motor function and muscle atrophy (Yue, 1995).

In 2001, a new formulation containing Cetylated fatty ester complex (CFEC; also known as Esterified fatty ester complex or EFAC) began to be used for arthritic and sports injury-related conditions. The underlying mechanisms of action were apparently associated with reduction of inflammation and cytokine activities (Perez-Jimenez et al., 1999; Hesslink et al., 2002; Diehl and May, 1994; Kraemer et al., 2004, 2005a,b). Fatty acids may induce changes in membrane fluidity, antibody and cytokine production (Grimble and Tappia, 1988), adhesion molecule expression (De Caterina et al., 2000) and signal transduction pathways, suppress leukocyte function (Kremer, 1996; James et al., 2000), trigger apoptosis (Heraud et al., 2000) and, like NSAIDs, reduce production of prostaglandins and leukotrienes (De Caterina et al., 2000; Kremer, 2000). Cetylated fatty acids reduce pain and stiffness, while increasing flexibility and range of motion for arthritic patients (Cochran and Dent, 1997; Siemandi, 1997; Hesslink et al., 2002; Kraemer et al., 2004, 2005a,b; Stammers et al., 1992). This study evaluated the effects of CFEC topical treatment with PT on patients with MPS of the neck.

Methods

Study population

A total of 74 participants were recruited as volunteers into the study, which was conducted at 8 sites of the RECOUP Neuromusculoskeletal Rehabilitation Centre in Bangalore, India. Males and females (age, 18–65 years) were selected having MPS of the neck for at least 2 weeks duration with $\geq$2 MTrPs in any one or more of the following: trapezius, sternocleidomastoid, anterior scalene, suboccipital or levator scapulae muscles. The diagnosis of MPS was made by an Orthopaedic/Rehabilitation Specialist (>10 years experience treating MPS) using the Simons Criteria (Simons et al., 1999), that required 5 major and at least 1 of 4 minor criteria to be satisfied.

Major criteria:

1. Localised spontaneous pain.
2. Spontaneous pain or altered sensations in expected referred pain area for given MTrP
3. Taut, palpable band in accessible muscle.
4. Exquisite, localised tenderness in precise point along taut band
5. Some measurable reduced movement range.

Minor criteria:

1. Reproduction of spontaneously perceived pain and altered sensations by pressure on MTrP.
2. Elicitation of local twitch response of muscular fibers by transverse ''snapping'' palpation or by needle insertion into MTrP.
3. Pain relief obtained by muscle stretching or injection of MTrP.
4. Electromyographic demonstration of spontaneous electrical activity characteristic of active loci in the tender nodule of a taut band.

Study duration including recruitment was seven months. 61 males and 11 females, ages 19–51, were selected (study retention rate = 98.2%). About 60% of patients in each group in this study had chronic conditions (lasting more than 3 months).

Exclusion criteria

a) Pregnancy or possible pregnancy during study, b) fibromyalgia, whiplash injury, degenerative or inflammatory arthritis of cervical areas, cervical radiculopathy or myelopathy, c) those having myofascial therapy or spinal manipulative therapy during past month, d) persons with articular instability or vertebrobasilar insufficiency, e) those allergic to topical cream components, f) individuals using immunosuppressive agents (DMARDs) and g) those taking NSAIDs or muscle relaxants and unwilling to give up for the study period plus 3 day pre-trial washout period. The IECR Board approved both protocol and informed consent. Prior to study, subjects were informed of study and treatments, and then signed a written consent form. This study adhered to principals of the Helsinki Declaration and its amendments in conformity with GCP principles.

Study design

The participants, given coded designations, were randomly assigned into two groups: a) topical CFEC cream application plus physical therapy (CF-PT; $n = 37$), and b) placebo cream application plus physical therapy (PL-PT; $n = 35$).

Assignments were made from a randomised list compiled prior to recruitment. Code assignments were not broken until after participants' results were obtained.

Based on assigned code, medications were given to all participants who were asked to apply it liberally to affected areas twice a day. All participants were shown how to apply and were queried at each session as to the success of compliance with applications. Compliance with only occasional miss of an application was estimated at $\geq$90%. Dose administration was regulated through amount of cream provided for participant use.

Physical therapy was administered to all through a sequenced protocol including, after evaluation: a) ischaemic compression (90—120 s) followed by a deep pressure soft tissue TrP massage to inactivate MTrPs, then b) myofascial release technique, which is a therapeutic treatment that uses gentle pressure and stretching to facilitate the release of fascial restrictions caused by accidents, injury, stress, repetitive use and traumatic or surgical scarring (LeBauer et al., 2008). Muscle energy techniques, articular mobilisations and neural mobilisations were also used subsequently, where required. Self stretching, relaxation and breathing exercises, ergonomics training and postural correction were also performed, followed by strength training and aerobic conditioning. A total of eight sessions of PT (2 sessions per week; 45 min/session) were given.

Topical treatments

CFEC cream formulation contained 8 cetylated fatty esters (5.6% w/w; decanoate, laurate, myristate, myristoleate, oleate, palmitate, palmitoleate and stearate) and 1.5% w/w menthol in a cream base (pH 6.5). Placebo cream had the same composition but without cetylated fatty esters. Tubes were marked similarly.

Study assessments

The study period (4 weeks) included 3 visits used to collect group and individual data. Planned visits (v1-3; week 0 or baseline, week 2 and week 4) were scheduled not to conflict with therapy. Information was collected for each visit by the therapist (symptoms, weight, BP, temperature, pulse and respiratory rate). The primary efficacy measures were changes from baseline week through final week of therapy in average Neck Disability Index (NDI; modified version of the Oswestry Low Back Pain Questionnaire; Vernon and Mior, 1991) and in the Neck Pain and Disability Visual Analogue Scale (NPDVAS; Wheeler et al., 1998; Carlsson, 1983). Secondary measures included algometer readings for each TrP, Cervical Range of Motion measurements (CROM®), tenderness to palpation and written participant responses to the 36-item short-form health survey (SF36; Ware and Sherbourne, 1992).

The Neck Disability Index (NDI) — 60 question functional outcome tool assessing neck related disability and disability due to neck pain with everyday activities. Sections evaluated pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping and recreation. For each category a 0—4 NDI indicated no disability while 35—50 NDI (50 is maximum) indicated complete disability.

The Neck Pain and Disability Visual Analogue Scale (NPDVAS) — measured disability related to pain in everyday life activities and functional limitations of the neck. 20 assessment questions used 10 cm visual analogue scales (VAS) to evaluate pain in 4 underlying dimensions: dysfunctional or disabling neck problems, pain intensity, affective aspects, and life activity interferences. Maximum score of 100 = most severe. Test reliability with retest reliability coefficient = 0.93 under controlled conditions (Wheeler et al., 1999).

The Algometer Pain Test® (from Wagner Instruments, USA) was performed upon prone subjects with TrP areas exposed. Pressure was applied perpendicularly and gradually through an algometer (1.0 cm^2 tip) at each palpated point. When subject verbally cued pain onset the pressure level was noted. An unaffected contra-lateral side or midline test served as control. Test sites were marked by pen for future reference. Palpation (0 = none, 1 = minimal, 2 = moderate, 3 = severe discomfort with minimal pressure) of the major MTrP was assessed prior to algometer testing.

The CROM® Instrument measured degrees of rotation, flexion, extension, and lateral bending.

The 36-item Short-Form Health Questionnaire (SF36) — assessed the health-related quality of life (HRQOL) effects of MPS on 8 QOL domains: bodily pain, physical functioning, role limitations due to physical problems, mental health, vitality, social functioning, role limitations due to emotional problems and general health. Scoring yielded values 0—100, with greater values representing greater QOL. A composite SF36 Index (8 domain total) was used to provide an overview as to the combined effects of all domains on QOL. This was done by summing individual domain scores, adjusted into a 0—100 scale.

Laboratory tests (complete blood counts and erythrocyte sedimentation rates) and radiographs of Cervical Spine (AP and Lateral views) were taken initially to rule out degenerative or inflammatory conditions of cervical spine and assess health.

Throughout the study, adverse events were monitored and reported, denoting seriousness, severity, action taken and relationship to study drug.

Statistical analysis

The questionnaire responses were analysed, assuming continuous data and an ordinal logistic regression, which estimates cumulative probability of being at or below each individual response level. All statistics were 2 tailed and significance was set at $p < 0.05$. Response differences within a group were evaluated by one way analysis of variance (ANOVA) with repeated visit measures. For comparisons between groups and for differences within groups at different visits, the nonparametric Mann—Whitney *U* Statistic Test for non-matched groups was used. For NPDVAS, palpation and NDI,

$$\%\,\text{Improvement}(\text{Relative Change from baseline}) = (1 - (\text{Mean}_{\text{Visit } n}/\text{Mean}_{\text{week } 0})) \times 100.$$

For Algometer Readings, SF36 Indices and CROM measurements,

$$\%\text{Improvement} = ((\text{Mean}_{\text{Visit } n}/\text{Mean}_{\text{week } 0}) - 1) \times 100,$$

where n = visit number and week 0 = visit 1.

A minimum estimated sample size for desired study results was 19.27 based on:

$$N = \left[\left(Z_\alpha(p_0(1-p_0))^{1/2} + Z_\beta(p_1(1-p_1))^{1/2}\right) \Big/ (p_1 - p_0)\right]^2$$

where:
N: Required sample size; Z_α: Z for two-sided alpha value of 0.05 (1.960); Z_β: Z for beta level of 0.20—0.80 power (0.842); p_0: Patient Proportion expected to have better response to placebo under null hypothesis (0.50); p_1: Expected patient proportion with better response to treatment (0.80).

Results

Table 1 depicts demographics for each group. Each group composition in regards to sex, and average age, weight and body mass index was relatively similar [for height ($p > 0.82$), BMI ($p > 0.30$), weight ($p > 0.33$) and age ($p > 0.10$)]. Scoring results at time of recruitment indicated that there was no significant difference between groups in regards to NPDVAS, and the mean measures would be categorised as moderate to severe neck pain.

Changes in neck disability with treatment

NDI

The primary efficacy measure showed that both treatment methods resulted in decreases in disability (Figure 1 and Table 2). At Week 0 (V1), mean NDIs of both groups were sufficiently high to be categorised as ''complete disability'' (CF-PT, 38.37; PL-PT, 36.24). By last visit, only CF-PT efficacy outcome was significant ($p < 0.001$) from baseline visit, indicating disability reductions due to treatment. While improvements were noted in the PL-PT group compared to baseline (by week 4, the mean index value improved to ''severe''), the changes were insignificant. By last visit, CF-PT treatment values were statistically significant compared to PL-PT group ($p < 0.001$). Mean NDI decreased two categories for the CF-PT group (18.8 = moderate disability) and one category for PL-PT (30.5).

Pain responses of test populations

NPDVAS analysis

The second primary efficacy measure showed that both treatments resulted in significant improvements from baseline for week 2 and week 4. The baseline average scores (±standard deviation) for PL-PT and CF-PT were high, 47.3 ± 7.2 and 46.3 ± 10.9, respectively, but not significantly different (Table 2). Improvement by both groups was progressive throughout study. NPDVAS results were significantly different from baseline for both groups by 2nd visit. However, most improvements observed were with CF-PT, which were also significantly different from PL-PT treatment by 2nd and 3rd visit. Treatment effects are shown in Figure 2.

Algometer and palpation responses

Both average algometer pain thresholds at the major MTrPs and palpation tenderness are given in Table 3. TrP readings show a greater sensitivity to pain than that of selected control regions. For both treatments, sensitivity decreased over the 4 week period but still maintained a lower threshold than that of control regions (average control threshold for all groups was 5.37 ± 0.17; no significant difference between groups). Palpations, performed on the major TrP (TrP1; usually in the trapezius muscle), confirmed tenderness in that area. PT provided increasing reductions in tenderness to palpation throughout the study, but with lack of notable additive effects for CF-PT.

SF36 body pain index

A subcategory of the SF36 Survey also provides participant feedback on effects of treatment on pain experienced. The SF36 body pain index indicated that participant pain was reduced over the treatment period by both the treatments. As shown (Table 4), average response/group suggested that CF-PT provided better and statistically significant pain management.

Changes in cervical spine range of motion with treatment

Both treatment groups increased the average range of motion (Table 3) but the greatest increases were in the areas of extension and flexion. For total rotation and total lateral movement, there were no significant differences between treatments; however, for flexion plus extension, CF-PT provided the greatest increases in movement, significant from that of PL-PT. Otherwise, CFEC topical treatment did not appear to have an additive effect on CROM changes beyond that of PT. The results for total CROM are shown graphically in Figure 3.

Disability-related quality of life — SF36 health survey

The SF composite index reflects all 8 domain values, but main contributions were pain, physical function and role

Table 1 Study group demographics.

Parameter	CF-PT group		PL-PT group	
	Male	Female	Male	Female
Number (%)	31 (83.8%)	6 (16.2%)	30 (85.7%)	5 (14.3%)
Average age (range)	29.9 (21—51)	32 (24—42)	28.4 (21—36)	26.8 (19—34)
Average weight (kg)	67.8	59	70.0	57.2
Average BMI	25.5	23.4	26.4	22.4
NPDVAS at recruitment screen (mean ± SD)	52.02 ± 10.17 $p = 0.928$		51.74 ± 12.94	

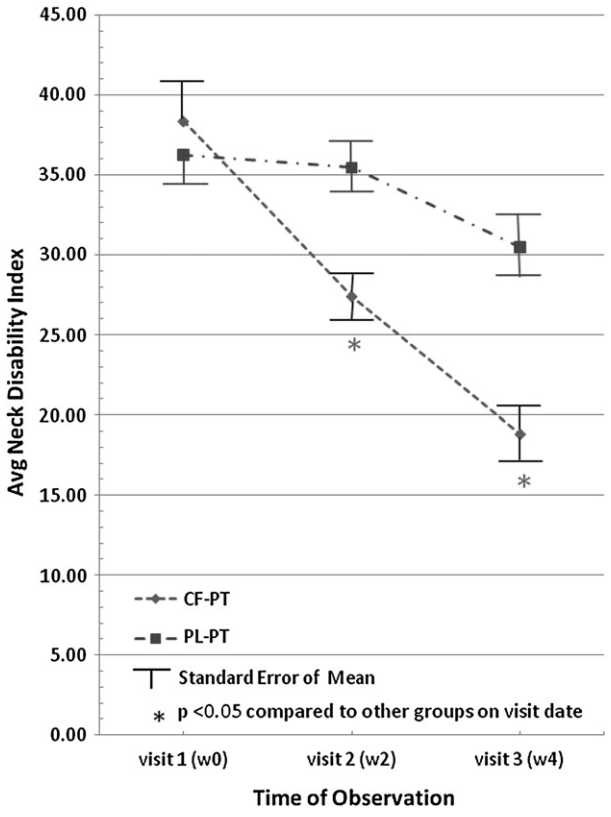

Figure 1 Treatment effects on neck disability index. A negative change indicates a more favorable result. Visit 1 is the baseline visit.

limitations due to physical problems (these observed by separate analyses of each domain; Table 4). Results (Figure 4) indicate that CF-PT treatment responses improved during treatment, while, at best, there was no notable change in overall QOL with PL-PT. In addition, CF-PT changes were significantly greater by visits 2 and 3 than PL-PT.

Normative data from a random sample of the Canadian population ($n = 9423$; age ≥ 25; male and female) was used for comparison (Hopman et al., 2000) to study responses (Table 4). As higher values represent a better QOL, the results of both groups in all 8 domains did not improve to that seen with the normative data and would suggest differences between these populations even at the end of our study (Canadian scores, however, were higher in most domains than US and European counterparts; Hopman et al., 2000). In general, CF-PT improved responses in 6 of 8 categories, suggesting a positive effect to QOL. Greatest % average improvements seen with CF-PT was for body pain, physical function, limitations in roles due to physical problems and limitations in roles due to emotional problems. Only with vitality responses were changes from baseline minimal with no observed difference between treatments.

The physical function index evaluates disability effects on daily functions [i.e., walking, climbing stairs, dressing and vigorous or moderate activities (heavy lifting, sports and moving objects)]. These results indicate physical function improvements were gained back by CF-PT, but there was no change in PL-PT.

Adverse events

No clinically significant events were associated with any treatment nor were adverse events noted as a result of PT. One of 72 patients (1.4%) treated with topical CFEC cream developed a hypersensitivity rash, which quickly resolved after treatment was discontinued. Likewise, there were no non-study events or events of clinical interest not related to the study that would have affected either group responses. Two patients did not complete the study: one developed the rash (indicated above) and the other tested positive for inflammatory arthritis just after study enrolment. Otherwise, no abnormal or alert level blood chemistry results were observed.

Discussion

The present study suggests that CFEC topical treatment can aid in the treatment of MPS by reducing debilitating symptoms. The inclusion of CFEC topical applications with PT resulted in significant increases in levels of pain reductions, improved neck disability assessments, reductions in TrP sensitivity and improvements in CROM.

Specifically, study analyses showed that for improvements in pain (NPDVAS and SF36 pain index), neck disability

Table 2 Primary outcome measures within groups and between groups.

Evaluation	Measure	Visit (week)	Efficacy assessment*				Significance between groups
			CF-PT	Significance from baseline	PL-PT	Significance from baseline	CF-PT vs PL-PT
Neck disability	NDI	0	38.4 ± 11.7	N/A	36.2 ± 11.2	N/A	0.475
		2	27.4 ± 6.3	<0.001	35.5 ± 8.9	0.858	<0.001
		4	18.8 ± 7.8	<0.001	30.5 ± 10.4	0.081	<0.001
Neck pain	NPD-VAS	0	46.3 ± 10.2	N/A	47.3 ± 7.3	N/A	0.386
		2	34.8 ± 7.4	0.003	43.2 ± 5.5	<0.001	<0.001
		4	25.3 ± 10.4	<0.001	34.0 ± 8.3	<0.001	<0.001

Mann–Whitney nonparametric two-tailed test; *significance = $p < 0.05$.
Treatments: CF-PT = CFEC with physical therapy; PL-PT = Placebo with physical therapy.

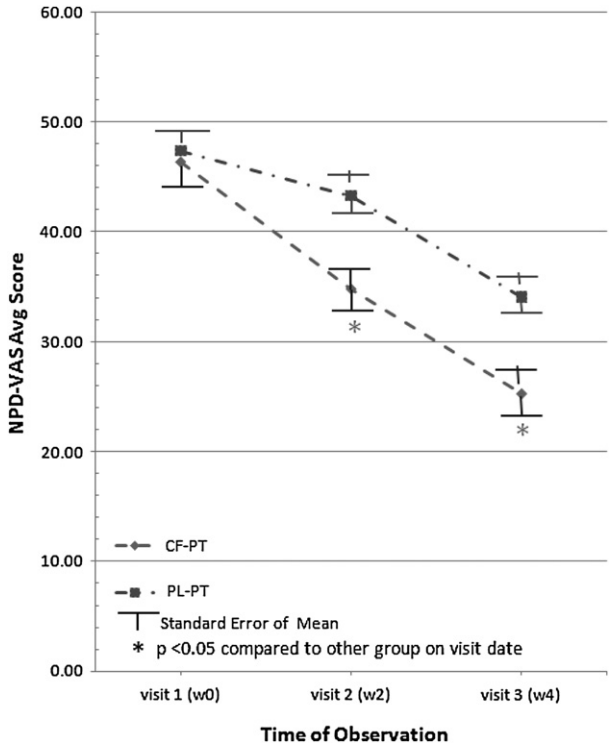

Figure 2 Treatment effects on neck pain & disability visual analogue scale indices. A negative change indicates a more favorable result. Visit 1 is the baseline visit.

(NDI), and life quality (6 of 8 SF36 categories), CF-PT was more effective than PL-PT. For indicators evaluated using the SF36 HRQOL Survey, it was evident that CF-PT had important effects on QOL improvement parameters, compared to PL-PT. Certainly, pain reductions associated with topical CFEC applications (as opposed to placebo cream applications) were critical in contributing to QOL and, when used in conjunction to PT, to improvements in response to PT. Compared to normative data, both groups registered at baseline the lowest QOL scores for pain, physical function, role limits due to physical problems, social functioning, role limits due to emotional problems, and, to some extent, general health. In all these areas, moderate to major improvements were found with CF-PT treatment compared to PL-PT. Our results of only small effects on mental health agree with earlier observations that MPS patients may have QOL profiles mostly affected by physical health (Tüzüm et al., 2004). But it has also been noted that anxiety and depression are frequent in long term MPS patients (Dohrenwend et al., 1999; Eden et al., 2000; Keefe and Dolan, 1986). The effects of CF-PT in reducing role limits due to emotional problems (visit 3 vs baseline, $p = 0.077$; CF-PT vs PL-PT at visit 3, $p = 0.010$) suggests some anxiety and depression factors may have been addressed with this treatment modality.

The addition of CFEC topical applications to physical therapy (CF-PT) provided the most effective treatment modality. This suggests that combining PT with CFEC topical application may address biochemical and pathophysiological abnormalities synergistically.

But for some areas, however, the addition of CFEC topical application to treatment did not improve responses. These areas were total CROM response, MTrPs palpation tenderness and MTrPs pain threshold pressure responses. Neck range of motion improved significantly compared to baseline, as did the reduction in pain and tenderness at the MTrPs, but with no significant difference between groups. CF-PT was statistically equivalent to PL-PT in total CROM and total lateral movement. It would appear that for these responses, PT addresses some underlying MPS factors, for which topical CFEC treatment is not additive. Physical manipulation of the affected muscle areas and exercise programs may be necessary to achieve proper responses desired. This contrasts to the pain, disability indicators and QOL, in which topical CFEC treatment did improve response. Our results concur with those of Gam et al. (1998; study treating MPS with ultrasound, massage and exercise) who found massage and exercise to reduce the number and intensity of MTrP. But they noted that MTrP reduction had little impact on the patients' neck and shoulder complaints (Gam et al., 1998). Further studies are needed to see if long term CFEC treatment only can reduce or eliminate active and/or latent MTrPs.

PT in this study was effective in treating participants' conditions (PL-PT improvements observed for pain reduction, TrP inactivation, disability reduction and improved range of motion). Patient histories at the Centre indicate that PT of several weeks reduces symptoms and improves the quality of life in both acute and chronic MPS cases equally well. Experience also suggests that without treatment, most MPS conditions continue, if not worsen with time.

For use in comparison with this study, the available non-anecdotal information on pharmaceutical approaches is limited. Few clinical trials lend support for various treatment usages (Aker et al., 1996). As in our study, most note with treatment decreases in pain with increased functional capacity and QOL.

a. Topical analgesics used include lidocaine patches (5%), EMLA cream (2.5% lidocaine and 2.5% prilocaine), bupivacaine MTrP injections, capsaicin cream (0.025% and 0.075%), and doxepin hydrochloride (Argoff, 2002; Affaitati et al., 2009; Dalpiaz and Dodds, 2001). Lidocaine iontophoresis (LIG) and direct current treatment of trigger points were both found to be effective treatment modalities but no difference was found if both were combined (Kaya et al., 2009). Bupivacaine injections may be accompanied by injection discomfort and high cardiotoxicity (Fine et al., 1988). And paresthesia and coldness/burning sensations were common side effects noted with lidocaine treatments.
b. Clonazepam has an antinociceptive effect for pain with chronic MPS (Fishbain et al., 2000). Similar analgesic effects have been reported for alprazolam (Russell et al., 1991), diazepam (Verma, 1982), midazolam (Serrao et al., 1992) and buprenorphine injections (particularly with significant neuropathic component present; Likar and Sittl, 2005). Opioids, however, may be addictive, with sedation a common side effect.
c. Clonidine and tizanidine (alpha$_2$ adrenergic agonists) have been used to increase nociceptive thresholds and inhibit spinal neuron response (Longmire, 1999). Side effects, however, may be high. In a tizanidine study showing efficacy (Malanga et al., 2002), 66% reported at least one adverse event (84% treatment related and

Table 3 Secondary outcomes measures within groups and between groups.

Evaluation	Subcategory	Visit (week)	Efficacy assessment[a]				Significance between groups[b]	
			CF-PT	% Average improvement	PL-PT	% Average improvement	CF-PT vs PL-PT	Observed significance in treatment response
Palpation	Average tenderness rating	0	2.10 ± 0.72	0.0	2.20 ± 0.65	0.0	0.692	Insignificant
		2	1.81 ± 0.51	13.8	1.92 ± 0.64	12.7	0.631	
		4	1.4 ± 0.60	33.3	1.56 ± 0.77	29.1	0.643	
Algometer TrP 1	Average pain threshold intensity	0	2.01 ± 0.48	0.0	2.23 ± 0.60	0.0	0.142	Insignificant
		2	2.41 ± 0.55	19.9	2.56 ± 0.57	14.8	0.277	
		4	2.96 ± 0.44	47.3	2.84 ± 0.56	27.4	0.785	
Algometer TrP 2	Average pain threshold intensity	0	2.06 ± 0.62	0.0	2.30 ± 0.58	0.0	0.122	Insignificant
		2	2.40 ± 0.65	16.5	2.59 ± 0.63	12.6	0.346	
		4	2.86 ± 0.55	38.8	2.83 ± 0.63	23.0	0.977	
CROM Measurements	Total rotation (average in degrees)	0	116.39 ± 14.09	0.0	119.30 ± 17.06	0.0	0.484	Insignificant
		2	119.11 ± 13.40	2.3	124.13 ± 16.86	4.0	0.216	
		4	124.86 ± 13.99	7.3	127.33 ± 16.91	6.7	0.548	
	Average flexion + extension (in degrees)	0	127.05 ± 30.18	0.0	115.07 ± 25.90	0.0	0.144	Significant difference
		2	133.55 ± 23.59	5.1	119.21 ± 23.75	3.6	0.037	
		4	138.64 ± 21.94	9.1	126.41 ± 20.76	9.9	0.050	
	Average total lateral (in degrees)	0	93.95 ± 11.63	0.0	91.69 ± 15.13	0.0	0.548	Insignificant
		2	101.64 ± 12.70	8.2	94.72 ± 13.57	3.3	0.068	
		4	106.00 ± 13.58	12.8	98.66 ± 12.40	7.6	0.054	

Treatments: CF-PT = CFEC topical with physical therapy; PL-PT = Placebo topical with physical therapy.
% Average Improvement = % change for that visit in average from baseline average.
[a] Efficacy Assessments are given as Mean $\pm$ SD.
[b] Mann–Whitney nonparametric two-tailed test; significance = $p < 0.05$.

Table 4 Quality of life measures from the SF36 HRQOL survey.

Scale	Normative population data	Visit (week)	Efficacy assessment[b]				Significance between groups[c]	
			CF-PT	% Average improvement	PL-PT	% Average improvement	CF-PT vs PL-PT	Observed significance in treatment response
Body Pain Index	78.0 ± 22.3[a]	0	45.0 ± 12.5	0.0	46.8 ± 12.7	0.0	0.794	Significant difference
		2	56.4 ± 10.8	25.3	45.3 ± 13.0	−3.1	<0.001	
		4	64.4 ± 13.2	42.9	48.2 ± 13.2	3.1	<0.001	
Physical Function Index	88.2 ± 18.4[a]	0	54.0 ± 15.3	0.0	63.0 ± 17.7	0.0	0.060	Inconclusive as to trend
		2	64.8 ± 19.2	20.1	58.8 ± 15.8	−6.7	0.014	
		4	70.5 ± 27.3	30.7	63.8 ± 18.6	1.2	0.058	
Role Limits due to Physical Problems Index	85.7 ± 30.2[a]	0	37.5 ± 31.8	0.0	43.9 ± 30.0	0.0	0.570	Significant difference
		2	57.3 ± 25.5	52.0	44.19 ± 24.9	0.6	0.042	
		4	68.3 ± 28.8	68.3	47.0 ± 21.4	7.1	0.003	
Mental Health Index	79.0 ± 14.7[a]	0	64.0 ± 15.4	0.0	65.4 ± 14.7	0.0	0.721	Significant difference
		2	68.0 ± 17.1	6.3	60.2 ± 12.5	−7.9	0.058	
		4	66.9 ± 15.9	4.6	58.1 ± 12.4	−11.3	0.024	
Vitality Index	68.9 ± 17.1[a]	0	58.5 ± 13.0	0.0	59.2 ± 11.3	0.0	0.699	Insignificant
		2	57.9 ± 9.4	−1.0	57.7 ± 7.2	−2.6	0.934	
		4	61.9 ± 8.5	5.9	56.8 ± 9.4	−4.1	0.110	
Social Functioning Index	88.3 ± 18.6[a]	0	59.3 ± 16.1	0.0	55.9 ± 17.4	0.0	0.442	Significant difference
		2	61.7 ± 16.1	4.1	51.0 ± 15.0	−8.7	0.012	
		4	68.5 ± 19.2	15.5	47.6 ± 14.6	−14.9	<0.001	
Role Limits due to Emotional Problems Index	87.0 ± 29.3[a]	0	52.5 ± 31.6	0.0	52.5 ± 30.2	0.0	0.982	Significant difference
		2	65.3 ± 32.1	24.4	42.4 ± 28.1	−19.2	0.012	
		4	69.2 ± 31.3	31.8	47.5 ± 25.2	−9.6	0.010	
General Health Index	77.6 ± 17.7[a]	0	55.7 ± 12.9	0.0	53.3 ± 11.3	0.0	0.466	Significant difference
		2	59.4 ± 12.3	6.6	49.4 ± 11.5	−7.4	0.002	
		4	61.2 ± 14.5	9.9	52.6 ± 10.2	−1.4	0.014	

Treatments: CF-PT = CFEC topical with physical therapy; PL-PT = Placebo topical with physical therapy.
% Average Improvement = % change for that visit in average from baseline average.
[a] Normative data from a random sampling of the Canadian population (Hopman et al., 2000).
[b] Efficacy Assessments are given as Mean ± SD.
[c] Mann–Whitney nonparametric two-tailed test; significance = $p < 0.05$.

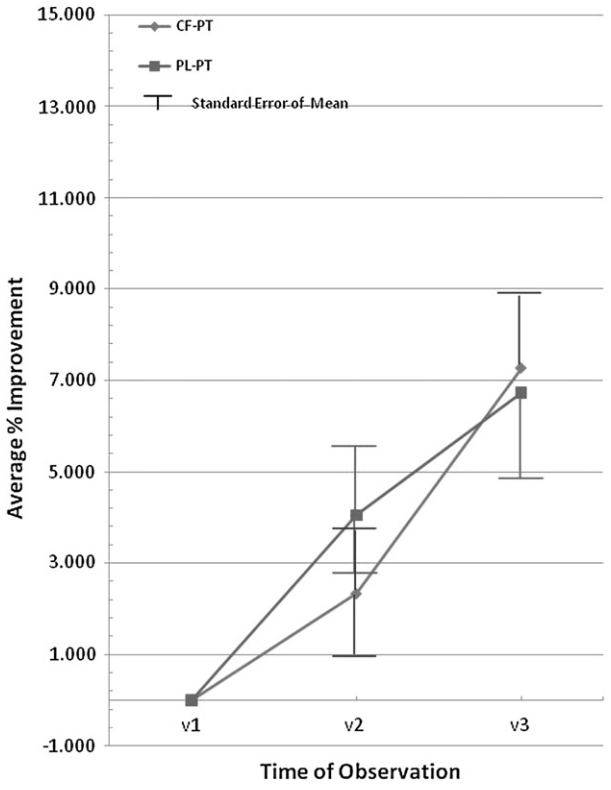

Figure 3 Treatment effects on total cervical range of motion. A positive change indicates a more favorable result. V1 = baseline visit; V2 = week 2 Visit; V3 = week 4 visit.

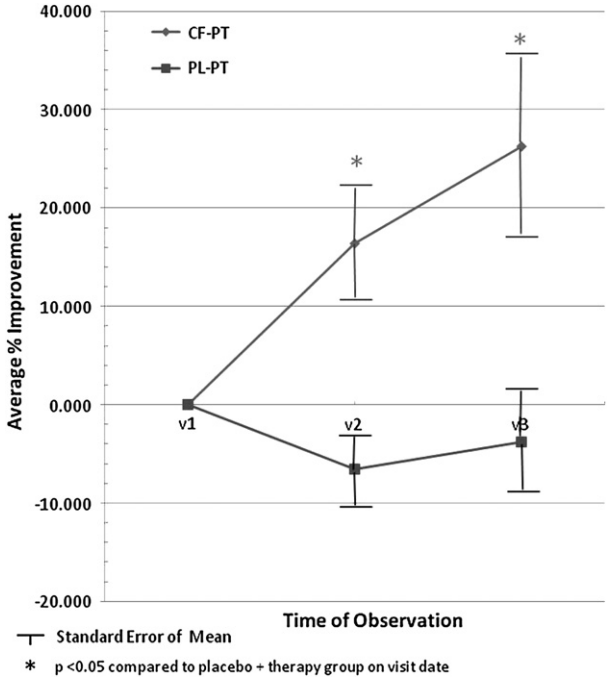

Figure 4 Changes in the composite SF36 QOL index with treatment. A positive change indicates a more favorable result. V1 = baseline visit; V2 = week 2 Visit; V3 = week 4 visit.

47% severe). Common tizanidine side effects were dry mouth, somnolence/sedation, asthenia and dizziness (Malanga et al., 2002).

d. Thiocolchicoside, a semi-synthetic derivative of colchicoside with muscle relaxant properties, was studied in a randomised trial (ointment, injection, both ointment and injection). Pain severity measured with VAS significantly improved after the third day in all groups. Side effects, including mild nausea and dizziness, were observed in 31% of the patients (Ketenci et al., 2009).

It is probable that the most effective treatment for MPS requires MTrP inactivation, restoring normal muscle length, and eliminating or correcting the factors that created/perpetuated the MTrPs in the first place (Gerwin, 2005). These factors are coupled with multifaceted physical and chemical neuromuscular alterations (Mense, 2003; Kuan et al., 2007; Shah and Gilliams, 2008; Cook and McCleskey, 2002; Sachs et al., 2002; Shah et al., 2005, 2008). Cytokine and chemokine levels play a crucial role, as they are elevated in muscle regions with active MTrPs but not in normal, uninvolved muscle regions or those in which MTrPs are present but latent (Shah et al., 2005, 2008; Shah and Gilliams, 2008). A well defined sequential cascade of cytokines/chemokines precedes hypernociception (sensitisation), associated with neuropathic pain (Ferreira et al., 1988; Cunha et al., 1991, 1992, 2005; Poole et al., 1999; Lorenzetti et al., 2002; Verri et al., 2006). Ischaemic compression relaxes an MTrP presumably by depriving the muscle of oxygen and glucose through compression of capillary vessels and other manual myofascial therapies possibly stimulate endorphin production or activate the off-cells that suppress nociceptive transmission centrally (Gerwin, 1993).

The basis for efficacy of CFEC topical applications in this study may be related to that postulated in studies of treatment for osteoarthritis (OA). Kraemer et al. (2004) showed significant improvements in reducing knee joint pain and inflammation with improved QOL using CFEC in a topical formulation (Kraemer et al., 2004) and comparable results also obtained for OA of elbow and wrist (Kraemer et al., 2005a). Similar to some CROM improvements noted in this study, Kraemer et al. (2005b) found that topical CFEC applications improved joint utilisation through more normalisation of postural stability and plantar pressure distribution in knee OA. These reports proposed that cetylated fatty esters may reduce chronic inflammation through suppression of proinflammatory cytokines. Reductions in leukotriene B4 release from neutrophils and monocytes, which modulate inflammation and cytokine release, have also been postulated (Curtis et al., 2000; Kremer, 1996, 2000). Myristoleic acid, cetylated in CFEC, has been implicated as an inhibitor of 5-lipoxygenase, a central enzyme in leukotriene synthesis (Iguchi et al., 2001). CFEC treatment may address alterations in MPS at cellular and chemical levels, while acting in conjunction with PT to improve overall treatment response. Equally important may be the absence (or at most rare/minimal) of side effects associated with this application, which contrasts with other applications, such as with prolonged NSAIDs usage, opioids and other injectibles noted above. Other studies of cetylated fatty ester treatment of

fibromyalgia have also given encouraging results (Dunstan et al., 1999; Edwards, 2007), and it is probable that conditions similar to MPS may also benefit [i.e., other repetitive strain injuries including tendonitis, carpal tunnel syndrome and epicondilitis lateralis (Visser and van Dieen, 2006)].

In summary, this may be the first double-blinded study to report that cetylated fatty esters can aid in treating and reducing pain and symptoms of MPS when combined with PT. Improvements of patient conditions were better in most measurements than PT with a placebo cream.

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Deepak Sharan has disclosed that he received a research grant and consulting fees from Cymbiotics, Inc.

Biju Nirmal Jacob received fees for his work in performing the study.

Jack Bookout is employed as Vice President of Cymbiotics, Inc.

Raj Barathur is President of Cymbiotics, Inc.

The study protocol at RECOUP was conducted entirely by Dr. Deepak Sharan and other Physicians and Physical Therapists. All diagnosis, treatment and interaction with the patients, clinical interventions, data collection and recording were performed by Dr Sharan and the RECOUP staff.

Drs Barathur's and Bookout's contributions to the study were in pre-launch, monitoring study progress that was based on data collection by RECOUP's Physicians and Therapists and in post-study analysis with the RECOUP staff after unblinding of the data. This approach was taken in order to avoid any bias.

References

Affaitati, G., Fabrizio, A., Savini, A., Lerza, R., Tafuri, E., Costantini, R., Lapenna, D., Giamberardino, M.A., 2009. A randomized, controlled study comparing a lidocaine patch, a placebo patch and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: evaluation of pain and somatic pain thresholds. Clinical Therapeutics 31 (4), 705—720.

Aker, P.D., Gross, A.R., Goldsmith, C.H., Peloso, P., 1996. Conservative management of mechanical neck pain: systemic overview and meta-analysis. British Medical Journal 313, 1291—1296.

Argoff, C.E., 2002. A review of the use of topical analgesics for myofascial pain. Current Pain and Headache Reports 6 (5), 375—378.

Carlsson, A.M., 1983. Assessment of chronic pain. Part 1: aspects of reliability and validity of the visual analog scale. Pain 16, 87—101.

Cheshire, W., Abashian, S., Mann, J., 1994. Botulinum toxin in the treatment of myofascial pain syndrome. Pain 59, 65—69.

Cochran, C., Dent, R., 1997. Cetyl myristoleate — a unique natural compound valuable in arthritis conditions. Townsend Letter for Doctors and Patients 168, 70—74.

Cook, S.P., McCleskey, E.W., 2002. Cell damage excites nociceptors through release of cytosol ATP. Pain 95, 41—47.

Cunha, F.Q., Lorenzetti, B.B., Poole, S., Ferreira, S.H., 1991. Interleukin-8 as a mediator of sympathetic pain. British Journal of Pharmacology 104 (3), 765—767.

Cunha, F.Q., Poole, S., Lorenzetti, B.B., Ferreira, S.H., 1992. The pivotal role of tumour necrosis factor alpha in the development of inflammatory hyperalgesia. British Journal of Pharmacology 107 (3), 660—664.

Cunha, T.M., Verri Jr., W.A., Silva, J.S., Poole, S., Cunha, F.Q., Ferreira, S.H., 2005. A cascade of cytokines mediates mechanical inflammatory hypernociception in mice. Proceedings of the National Academy of Science — USA 102, 1755—1760.

Curtis, C.L., Hughes, C.E., Flannery, C.R., Little, C.B., Harwood, J.L., Caterson, B., 2000. n-3 Fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. Journal of Biological Chemistry 275 (2), 721—724.

Dalpiaz, A.S., Dodds, T.A., 2001. Myofascial pain response to topical lidocaine patch therapy. Journal of Pain and Palliative Care Pharmacotherapy 16 (1), 99—104.

De Caterina, R., Liao, J.K., Libby, P., 2000. Fatty acid modulation of endothelial activation. American Journal of Clinical Nutrition 71, 213S—223S.

Diehl, H.W., May, E.L., 1994. Cetyl myristoleate isolated from swiss albino mice: an apparent protective agent against adjubane arthritis in rats. Journal of Pharmaceutical Science 83, 296—299.

Dohrenwend, B.P., Raphael, K.G., Marbach, J.J., Gallagher, R.M., 1999. Why is depression comorbid with chronic myofascial face pain? A family study test of alternative hypotheses. Pain 83 (2), 183—192.

Dunstan, H.R., McGregor, N.R., Watkins, J.A., Konohoe, M., Roberts, T.K., Butt, H.L., Murdoch, R.N., Taylor, W.G., 1999. Changes in plasma lipid homeostasis observed in chronic fatigue syndrome patients. Journal of Nutritional and Environmental Medicine 9 (4), 267—280.

Eden, L., Ejlertsson, G., Leden, I., Nordbeck, B., 2000. High rates of psychosomatic and neurotic symptoms among disability pensioners with musculoskeletal disorders. Journal of Musculoskeletal Pain 8, 75—88.

Edwards, A.M., 2007. CMO (Cerasomol-cis-9-Cetyl Myristoleate) in the treatment of fibromyalgia: an open pilot study. Journal of Nutritional and Environmental Medicine 11, 105—111.

Ferreira, S.H., Lorenzetti, B.B., Bristow, A.F., Poole, S., 1988. Interleukin-1 beta as a potent hyperalgesic agent antagonized by a tripeptide analogue. Nature 334 (6184), 698—700.

Fine, P.G., Milano, R., Hare, B.D., 1988. The effects of myofascial trigger point injections are naloxone reversible. Pain 32, 15—20.

Fishbain, D.A., Goldberg, M., Meagher, B.R., Steele, R., Rosomoff, H., 1986. Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. Pain 26, 181—197.

Fishbain, D.A., Cutler, R.B., Rosomoff, H.L., Rosomoff, R.S., 2000. Clonazepam open clinical treatment trial for myofascial pain syndrome associated chronic pain. Pain Medicine 1 (4), 332—339.

Fricton, J.R., 1989. Myofascial pain syndrome. Neurologic Clinics 7, 413—427.

Frobb, M.K., 2003. Neural acupuncture: a rationale for the use of lidocaine infiltration at acupuncture points in the treatment of myofascial pain syndromes. Medical Acupuncture Journal for Physicians by Physicians 15 (1), 18—22.

Gam, A.N., Warming, S., Larsen, L.H., Jentsen, B., Hoydalsmo, O., Allon, I., Andersen, B., Gotzsche, N., Petersen, M., Mathiesen, B., 1998. Treatment of myofascial trigger-points with ultrasound combined with massage and exercise — a randomized controlled trial. Pain 77, 73—79.

Gerwin, R.D., 1993. The management of myofascial pain syndromes. Journal of Musculoskeletal Pain 1 (3/4), 83—94.

Gerwin, R.D., Dommerholt, J., Shah, J.P., 2004. An expansion of Simons' integrated hypothesis of trigger point formation. Current Pain and Headache Reports 8, 468—475.

Gerwin, R.D., 2005. A review of myofascial pain and fibromyalgia — factors that promote their persistence. Acupuncture in Medicine 23 (3), 121—134.

Grimble, R.F., Tappia, P.S., 1988. Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids. Zeitschrift fur Ernahrungswissenschaft 37, 57—65.

Grosshandler, S.L., Stratas, N.E., Toomey, T.C., Gray, W.F., 1985. Chronic neck and shoulder pain: focusing on myofascial origins. Postgraduate Medicine 77, 149—158.

Heraud, F., Heraud, A., Harmand, M.F., 2000. Apoptosis in normal and osteoarthritic human articular cartilage. Annals of Rheumatic Disease 59, 959—965.

Hesslink, R., Armstrong, D., Nagendran, M.V., Sreevatsan, S., Barathur, R., 2002. Cetylated fatty acids improve knee function in patients with osteoarthritis. Journal of Rheumatology 29, 1708—1712.

Hong, C.Z., 2002. New trends in myofascial pain syndrome. Chinese Medical Journal (Taipei) 65, 501—512.

Hopman, W.M., Towheed, T., Anastassiades, T., Tenenhouse, A., Poliquin, S., Berger, C., Joseph, L., Brown, J.P., Murray, T.M., Adachi, J.D., Hanley, D.A., Papadimitropoulous, E., 2000. Canadian normative data for the SF-36 health survey. Canadian Multicentre Osteoporosis Study Research Group. Canadian Medical Association Journal 163, 265—271.

Hou, C.R., Tsai, L.C., Cheng, K.F., Chung, K.C., 2002. Immediate effects of various physical therapeutic modalities on cervical myofascial pain and trigger-point sensitivity. Archives of Physical Medicine and Rehabilitation 83, 1406—1414.

Huguenin, L.K., 2004. Myofascial trigger points: the current evidence. Physical Therapy in Sport 5, 2—12.

Iguchi, K., Okumura, N., Usui, S., Sajiki, H., Hiroata, K., Kiran, K., 2001. Myristoleic acid, a cytotoxic component in the extract from serenoa repens, induces apoptosis and necrosis in human prostatic LNCaP cells. Prostate 47, 59—65.

James, M.J., Gibson, R.A., Cleland, L.G., 2000. Dietary polyunsaturated fatty acids and inflammatory mediator production. American Journal of Clinical Nutrition 71 (Suppl.), 343S—348S.

Kaya, A., Kamanli, A., Ardicoglu, O., Ozgocmen, S., Ozkurt-Zengin, F., Bayik, Y., 2009. Direct current therapy with/without lidocaine iontophoresis in myofascial pain syndrome. Bratisl Lek Listy 110 (3), 185—191.

Keefe, F.J., Dolan, E., 1986. Pain behavior and pain coping strategies in low back pain and myofascial pain dysfunction syndrome patients. Pain 24 (1), 49—56.

Ketenci, A., Basat, H., Esmaeilzadeh, S., 2009. The efficacy of topical thiocolchicoside (Muscoril) in the treatment of acute cervical myofascial pain syndrome: a single-blind, randomized, prospective, phase IV clinical study. Agri 21 (3), 95—103.

Kraemer, W.J., Ratames, N.A., Anderson, J.M., Maresh, C.M., Tiberio, D.P., Joyce, M.E., Messinger, B.N., French, D.N., Sharman, M.J., Rubin, M.R., Gomez, A.L., Volek, J.S., Hesslink Jr., R.L., 2004. Effect of a cetylated fatty acid topical cream on functional mobility and quality of life of patients with osteoarthritis. Journal of Rheumatology 31, 767—774.

Kraemer, W.J., Ratamess, N.A., Maresh, C.M., Anderson, J.A., Tiberio, D.P., Joyce, M.E., Messinger, B.N., French, D.N., Sharman, M.J., Rubin, M.R., Gomez, A.L., Silvestre, R., Hesslink Jr., R.L., 2005a. Fatty acid topical cream with menthol reduces pain and improves functional performance in individuals with osteoarthritis. Journal of Strength and Conditioning Research 19 (2), 475—480.

Kraemer, W.J., Ratamess, N.A., Maresh, C.M., Anderson, J.A., Tiberio, D.P., Joyce, M.E., Messinger, B.N., French, D.N., Sharman, M.J., Rubin, M.R., Gomez, A.L., Volek, J.S., Silvestre, R., Hesslink Jr., R.L., 2005b. Effects of treatment with a cetylated fatty acid topical cream on static postural stability and plantar pressure distribution in patients with knee osteoarthritis. Journal of Strength and Conditioning Research 19 (1), 115—121.

Kremer, J., 1996. Effects of modulation of inflammatory and immune parameters in patients with rheumatic and inflammatory disease receiving dietary supplementation of N-3 and N-6 fatty acids. Lipids 31 (Suppl.), S243—S247.

Kremer, J.M., 2000. N-3 Fatty acid supplement in rheumatoid arthritis. American Journal of Clinical Nutrition 71, 349S—351S.

Kuan, T.S., Hong, C.Z., Chen, J.T., Chen, S.M., Chien, C.H., 2007. The spinal cord connections of the myofascial trigger spots. European Journal of Pain 11 (6), 624—634.

LeBauer, A., Brtalik, R., Stowe, K., 2008. The effect of myofascial release (MFR) on an adult with idiopathic scoliosis. Journal of Bodywork and Movement Therapies 12 (4), 356—363.

Likar, R., Sittl, R., 2005. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. Anesthesia and Analgesia 100, 781—785.

Longmire, D.R., 1999. The relationship between the sympathetic nervous system and chronic myofascial pain has led to the use of the term chronic neuro-muscular pain (CNMP). In: American Academy of Pain Management Annual Meeting: Pain Management: A Decade of Integrating Clinical Services; Sept 24; Las Vegas (NV).

Lorenzetti, B.B., Veiga, F.H., Canetti, C.A., Poole, S., Cunha, F.Q., Ferreira, S.H., 2002. Cytokine-induced neutrophil chemoattractant 1 (CINC-1) mediates the sympathetic component of inflammatory mechanical hypersensitivitiy in rats. European Cytokine Network 13 (4), 456—461.

Maigne, R., 1996. Diagnosis and treatment of pain of vertebral origin, first ed. Williams and Wilkins, pp. 175—515.

Malanga, G.A., Gwynn, M.W., Smith, R., Miller, D., 2002. Tizanidine is effective in the treatment of myofascial pain syndrome. Pain Physician 5 (4), 422—432.

Mense, S., 2003. The pathogenesis of muscle pain. Current Pain and Headache Reports 7, 419—425.

Perez-Jimenez, F., Castro, P., Lopez-Miranda, J., 1999. Circulating levels of endothelial function are modulated by dietary monounsaturated fat. Atherosclerosis 145, 351—358.

Poole, S., Lorenzetti, B.B., Cunha, J.M., Cunha, F.Q., Ferreira, S.H., 1999. Bradykinin B1 and B2 receptors, tumour necrosis factor alpha and inflammatory hyperalgesia. British Journal of Pharmacology 126, 649—656.

Russell, I.J., Fletcher, E.M., Michalek, J.E., McBroom, P.C., Hester, G.G., 1991. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam: a double-blind, placebo-controlled study. Arthritis Rheum 34, 552—560.

Qerama, E., Fuglsang-Frederiksen, A., Kasch, H., Bach, F.W., Jensen, T.S., 2006. A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. Neurology 67 (2), 241—245.

Sachs, D., Cunha, F.Q., Poole, S., Ferriera, S.H., 2002. Tumor necrosis factor-a, interleukin-1B and interleukin-8 induce persistent mechanical nociceptor hypersensitivity. Pain 96, 89—97.

Serrao, J.M., Marks, R.L., Morley, S.J., et al., 1992. Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. Pain 48, 5—12.

Shah, J.P., Phillips, T.M., Danoff, J.V., Gerber, L., 2005. An in vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. Journal of Applied Physiology 99, 1977—1984.

Shah, J.P., Danoff, J.V., Desai, M.J., Parikh, S., Nakamura, L.Y., Phillips, T.M., Gerber, L.H., 2008. Biochemicals associated with

pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Archives of Physical Medicine and Rehabilitation 89, 16—23.

Shah, J.P., Gilliams, E.A., 2008. Uncovering the biochemical milieu of myofascial trigger points using in vivo microdialysis: an application of muscle pain concepts to myofascial pain syndrome. Journal of Bodywork and Movement Therapies 12, 371—384.

Siemandi, H., 1997. The effect of cis-9-myristoleate (CMO) and adjunctive therapy on arthritis and autoimmune disease — a randomized trial. Townsend Letter for Doctors and Patients 169/170, 58—63.

Simons, D.G., 1995. Myofascial pain syndrome: one term but two concepts: a new understanding. Journal of Musculoskeletal Pain 3 (1), 7—13.

Simons, D.G., Travell, J.G., Simons, L.S., 1999. Travell & Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual, second ed. Williams & Wilkins, Baltimore, p. 132.

Stammers, T., Sibbald, B., Freeling, P., 1992. Efficacy of cod liver oils an adjunct to non-steroidal anti-inflammatory drug treatment in the management of osteoarthritis in general practice. Annals of the Rheumatic Diseases 51, 128—129.

Tüzüm, E.H., Albayrak, G., Eker, L., Sözay, S., Daşkapan, A., 2004. A comparison study of quality of life in women with fibromyalgia and myofascial pain syndrome. Disability and Rehabilitation 26 (4), 198—202.

Verma, R.S., 1982. Diazepam and suxamethonium muscle pain (a dose-response study). Journal of the Association of Anaesthetists of Great Britain and Ireland 37 (6), 688—690.

Vernon, H., Mior, S., 1991. The neck disability index: a study of reliability and validity. Journal of Manipulative and Physiological Therapeutics 14, 409—415.

Verri, W.A., Cunha, T.M., Parada, C.A., Poole, S., Cunha, F.Q., Ferriera, S.H., 2006. Hypernociceptive role of cytokines and chemokines: targets for analgesic drug development? Pharmacology and Therapeutics 112, 116—138.

Visser, B., van Dieen, J.H., 2006. Pathophysiology of upper extremity muscle disorders. Journal of Electromyography and Kinesiology 16 (1), 1—16.

Ware, Je, Sherbourne, C.D., 1992. The MOS 36-Item Short-Form health Survey (SF-36). Medical Care 30, 473—483.

Wheeler, A.H., Goolkasian, P., Baird, A.C., Darden, B.V., 1999. The development of the neck pain and disability scale: item analysis, face, and criterion-related validity. Spine 24, 1290—1294.

Wheeler, A.H., Goolkasias, P., Gretz, S.S., 1998. A randomized double-blind prospective pilot study of botulinum toxin injection for refractory, unilateral, cervicothoracic, paraspinal myofascial pain syndrome. Spine 23, 1662—1667.

Wolfe, F., Simons, D.G., Fricton, J., Bennett, R.M., Goldenberg, D.L., Gerwin, R., Hathaway, D., McCain, G.A., Russell, I.J., Sanders, H.O., Skootsky, S., 1992. The fibromyalgia and myofascial pain syndromes: a preliminary study of tender points and trigger points in persons with fibromyalgia, myofascial pain syndrome and no disease. Journal of Rheumatology 19 (6), 944—951.

Yue, S.K., 1995. Initial experience in the use of botulinum toxin A for the treatment of myofascial related muscle dysfunctions. Journal of Musculoskeletal Pain 3 (Suppl. 1), 22.