Rheumatol Int (2013) 33:2665–2670
DOI 10.1007/s00296-012-2490-5

SHORT COMMUNICATION

Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients

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Received: 14 February 2012 / Accepted: 13 July 2012 / Published online: 28 July 2012

Abstract The purpose of this study was to evaluate the short-term efficacy of topical capsaicin treatment in patients severely affected by fibromyalgia. One hundred and thirty fibromyalgia patients were randomly divided into two groups. The control group, 56 women and 4 men who continued their medical treatment, and the capsaicin group, 70 women who apart from continuing their medical treatment, also underwent topical capsaicin 0.075 % 3 times daily for 6 weeks. At the beginning of the program, there were no significant differences between the two groups in any of the analyzed parameters. At the end of the treatment, there were significant improvements in the capsaicin group in the myalgic score (5.21 vs 3.8, $p = 0.02$) and global subjective improvement (22.8 vs 5 %, $p = 0.001$). Six weeks after the end of the treatment, the experimental group showed significant differences in Visual Analogue Scale of depression (5.63 vs 7.35, $p = 0.02$), Fibromyalgia Impact Questionnaire (67.89 vs 77.7, $p = 0.02$), role limitations due to emotional problems (36.17 vs 17.2, $p = 0.05$), Fatigue Severity Scale (6.2 vs 6.6, $p = 0.04$), myalgic score (3.94 vs 2.66, $p = 0.02$) and pressure pain threshold (79.25 vs 56.71, $p = 0.004$). In conclusion, patients severely affected by fibromyalgia can obtain short-term improvements following topical capsaicin 0.075 % treatment three times daily for 6 weeks.

Keywords Fibromyalgia · Capsaicin therapy
Chronic pain · Clinical assessment

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Introduction

Fibromyalgia (FM) is a syndrome of unknown etiology, characterized by chronic and diffuse musculoskeletal pain, which is demonstrated upon palpation of a series of characteristic points, associated with numerous other symptoms. The diagnosis is performed according to the classification criteria established in 1990 by the American College of Rheumatology (ACR) [1]. The pathophysiology is unknown, but evidence suggests that FM is associated with aberrant central nervous system (CNS) processing of pain and other stimuli [2]. Substance P (SP) is a neuromodulator neuropeptide widely distributed in the periphery and the CNS where is colocalized with other neurotransmitters such as serotonin or dopamine. SP has been proposed to play a role in the pathogenesis of pain syndromes, including FM [3]. Cerebrospinal fluid levels (CSF) of SP [4] are three to four times higher in FM patients.

Capsaicin (CAP), an alkaloid derived from hot chilli peppers from the genus Capsicum, interacts with sensory afferents via vanilloid receptors causing an initial

excitation of the neurones and a period of enhanced sensitivity. This is usually perceived as itching, pricking or burning, with cutaneous vasodilation due to selective stimulation of afferent C fibres and release of SP. This effect is followed by a refractory period with reduced sensitivity. Repeated applications lead to persistent desensitization possibly due to depletion of substance P [5] at nervous afferents endings and transiently decrease the density of nervous fibers on the skin. Topical creams with capsaicin 0.025–0.075 % 3–4 times daily for 6–8 weeks have been used to treat chronic musculoskeletal or neuropathic pain including chronic nonspecific back pain, postherpetic neuralgia, diabetic neuropathy, osteoarthritis, chronic neck pain, postsurgical pain, Guillain–Barré syndrome and rheumatoid arthritis [6, 7].

Since patients with chronic rheumatic pain syndromes often have a lower threshold for capsaicin-induced flare response, the purpose of the present study was to determine the efficacy of a capsaicin 0.075 % gel application, 3 times daily for 6 weeks, as a complementary treatment of severely affected FM patients. In addition, we assessed whether this procedure might still yield some clinical improvement 6 weeks after the discontinuation of this topical therapy.

Methods

Design

A 2-armed randomized trial was conducted. FM patients were randomly assigned to either topic capsaicin 0.075 % or usual treatment.

The primary outcome was overall score of pain. Secondary outcomes were several other FM-related variables. Baseline measurements were performed after eligibility (at week 0), and patients were subsequently allocated to one of the 2 study arms. Patients were instructed to keep taking the usual treatment, being excluded if they had medication changes during the trial. Therefore, patients were assessed at the start and at the end of the 6-week intervention period (this time considered as end of intervention). Finally, patients were again evaluated 6 week later (at week 12 after the onset of the study). Changes in outcome variables from pre-intervention (at week 0) to the end of follow-up were assessed.

Participants

For the inclusion in the study, patients had to be 18 years or older and fulfill the ACR 1990 criteria for FM [1], according to a diagnosis made by a Rheumatologist. They should have failed to achieve improvement following other treatments including nonsteroidal anti-inflammatory drugs, major opioids, tricyclic antidepressants (amitriptyline or cyclobenzaprine), selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, anticonvulsant drugs such as pregabalin and some other multidisciplinary therapies. Exclusion criteria were medical or psychiatric disorders. Informed consent was obtained, and then baseline data were collected. Afterward, FM patients were randomly assigned to one of the two different treatment groups by a computer-generated sequence prior to enrollment.

The study questionnaires and protocol were approved by the Ethical Committee of the regional health authority.

Interventions

Topical capsaicin group: Patients from the experimental group received topical administration of capsaicin 0.075 % (Sensedol®) over the 18 tender points 3 times daily in this controlled study during a 6-week period.

Patients from the control group kept on taking the same medical treatment that they received before randomization.

Assessment

Demographic and pain-related variables: Each participant was interviewed and asked to provide information about a number of demographic and pain-related variables including marital status, employment status and education.

They were also assessed on other clinical outcomes such us years until diagnosis, body mass index (BMI) and the number of physical symptoms that were obtained from a standardized symptom checklist. This self-report checklist instructed participants to indicate whether they experienced each one of 79 symptoms for at least 3 months over the past year before the study. A score was obtained by totaling the affirmative responses to all 79 symptoms.

The myalgic score, using a dolorimeter (Algometer Force Dial FDK 10. Wagner Instruments. P.O.B. 1217 Greenwich CT 06836 USA) upon 6 TP: Sites- supraspinous, second rib and epicondyle, bilaterally.

The pressure pain threshold: Assessed by sphygmomanometer as previously described [8]. The grip strength test assessed using the American Society of Hand Therapists recommendations. The 6-min walk test (ProAction. BH Fitness. G 648 Columbia). Visual Analogue Scale (VAS) of pain, fatigue, anxiety and depression (intensity experienced between 0 and 10 at the time that they were interviewed).

McGill Pain Questionnaire (MPQ) in the validated Spanish version [9].

Brief Pain Inventory (BPI) [10]. Fatigue Severity Scale (FSS) [11]. Pittsburgh Sleep Quality Index (PSQI)

validated in Spanish population [12]. Beck Anxiety Inventory (BAI) [13]. Beck Depression Inventory (BDI) [14]. Pain Catastrophizing Scale (PCS): a self-administered 13-item questionnaire that assesses rumination, magnification and helplessness. Each item is scored from 0 (not at all) to 4 (always), and the total score ranges from 0 to 52. We used the Spanish validated version [15]. Fibromyalgia Impact Questionnaire (FIQ): A 10-item self-report questionnaire developed to measure the health status of FM patients. We used the Spanish validated version [16]. Stanford Health Assessment Questionnaire (SHAQ) [17]. Medical Outcomes Survey Short Form-36 (SF-36): self-report questionnaire that explores 8 dimensions of physical and mental health status. The range of scores for each dimension varies from 0 to 100, and there are normalized reference values for the Spanish population. London Handicap Scale (LHS): To measure the level of functional impairment in patients with chronic, multiple or progressive diseases [18].

At the end of the therapy (at week 6), patients of both groups were asked for global subjective improvement that was defined as decrease in pain $\geq$30 %, improvement in physical function $\geq$10 % and improvement in sleep or fatigue $\geq$30 %.

Statistical analysis

Categorical variables are presented as number (%), and quantitative variables as mean $\pm$ standard deviation. Differences between basal variables were tested via Fisher's exact test for categorical variables and Student's t test for quantitative variables.

The effect of treatment on the different questionnaires performed in the follow-up was tested using analysis of covariance (ANCOVA), adjusting for gender, age and basal measure. All statistical analyses were performed with the software Stata 12/SE (Stata Corporation, College Station, TX, US). p values <0.05 were considered significant.

Results

Patients

From a series of 146 patients, 6 were not eligible because they did not fulfill the inclusion criteria, 10 declined to participate, and 130 patients agreed and were enrolled in the study: 60 were randomly assigned to the control group and 70 to the capsaicin group. A total of 108 (83.1 %) patients completed the study: 50 (83.3 %) from the control group and 58 (82.9 %) in the capsaicin group. The most common reasons for discontinuation were adverse effects, in most cases due to capsaicin (7 cases).

The mean $\pm$ SD age of participants was 52.29 $\pm$ 9.32 years; the mean delay to FM diagnosis was 9.3 $\pm$ 8.12 years, and the average reported in FIQ was 73.81. Most of them were married, had a primary level education, reported a moderate physical activity and did not drink or smoke.

Table 1 Baseline data after randomization

Outcome variables	Capsaicin (CAPG) Mean (SD)	Control Group (CG) Mean (SD)	p
Female/male ratio	70 female	56 female/4 male	
Abandon/dropout	12	10	
Years until diagnosis	12.13 (10.26)	10.08 (7.74)	
Age	53.57 (9.18)	50.82 (9.36)	0.1
Body mass index	27.36 (5.31)	28.15 (5.61)	0.4
Number of physical symptoms	48.18 (15.81)	49.08 (13.90)	0.7
Visual Analogue Scale (VAS) of depression	6.89 (2.96)	6.38 (2.96)	0.3
VAS of pain	8.2 (1.36)	7.96 (1.20)	0.3
VAS of anxiety	7.38 (2.55)	7.37 (2.24)	0.9
VAS of fatigue	9.05 (1.28)	8.71 (1.39)	0.1
Beck depression inventory	25.8 (11.09)	26.7 (11.04)	0.6
Fibromyalgia Impact Questionnaire	74.3 (15.38)	73.3 (13.84)	0.7
Stanford Health Assessment Questionnaire	1.68 (0.58)	1.68 (0.5)	0.9
Physical functioning	26.52 (18.8)	26.56 (15.6)	0.9
Role limitations due to physical problems	5.36 (21.16)	5.73 (18.04)	0.9
Pain (SF-36)	15.62 (13.72)	17.29 (13.54)	0.5
General health	19.02 (14.62)	22.4 (11.98)	0.2
Vitality	11.7 (15.47)	12.29 (13.68)	0.8
Social functioning	37.05 (25.55)	36.45 (27.63)	0.9
Role limitations due to emotional problems	24.39 (39.93)	24.99 (38.58)	0.9
Mental health	39.78 (21.45)	39.21 (21.24)	0.8
Fatigue Severity Scale	6.31 (1.02)	6.46 (0.74)	0.4
Beck Anxiety Inventory	34.75 (13.51)	35.06 (11)	0.8
Pittsburgh Sleep Quality Index	13.64 (4.24)	14.42 (3.64)	0.3
McGill Pain Questionnaire	41.83 (8.46)	42.44 (6.86)	0.6
Pain Catastrophizing Scale	36.33 (12.26)	34.07 (12.95)	0.3
London Handicap Scale	59.27 (14.04)	59.76 (11.68)	0.8
Pain intensity (BPI)	7.06 (1.67)	6.93 (1.31)	0.6
Level of interference (BPI)	7.47 (1.74)	7.43 (1.67)	0.9
Myalgic score	4.30 (3.39)	3.67 (2.21)	0.2
Pressure pain threshold	79.25 (44.69)	76.37 (33.43)	0.7
Grip strength	77.43 (31.15)	87.52 (40.13)	0.1
Six-minute walk test	97.1 (96.44)	76.25 (72.39)	0.2

BPI Brief Pain Inventory, *CAPG* capsaicin group, *CG* control group, *SD* standard deviation, *SF-36* short-form 36 health survey questionnaire, *VAS* Visual Analogue Scale

Table 2 Change in treatment outcome variables at the end of treatment and after 6-week follow-up

Outcome variables	Post-treatment CAPG Mean (SD)	Post-treatment CG Mean (SD)	*p*	Follow-up CAPG Mean (SD)	Follow-up CG Mean (SD)	*p*
Number of physical symptoms	48.69 (15.05)	50.89 (17.32)	0.5	48.17 (18.5)	53.19 (15.51)	0.2
VAS of depression	6.69 (2.88)	6.62 (3.12)	0.9	5.63 (3.11)	7.35 (3.11)	0.02
VAS of pain	7.97 (1.69)	7.96 (1.29)	0.9	7.74 (1.77)	8.06 (1.31)	0.4
VAS of anxiety	7.08 (2.77)	6.97 (2.65)	0.8	6.77 (2.94)	7.84 (2.68)	0.1
VAS of fatigue	8.69 (1.28)	8.72 (1.3)	0.9	8.51 (2.04)	9 (1.12)	0.2
Beck Depression Inventory	26.5 (11.43)	27.14 (11.21)	0.8	23.41 (11.53)	27.13 (9.4)	0.1
Fibromyalgia Impact Questionnaire	72.5 (13.06)	74.25 (13.94)	0.5	67.89 (18.7)	77.7 (16.37)	0.02
Stanford Health Assessment Questionnaire	1.61 (0.61)	1.61 (0.57)	0.9	1.53 (0.7)	1.71 (0.57)	0.2
Physical functioning	28.46 (15.31)	28.79 (14.97)	0.9	31.14 (18.75)	28.55 (17.23)	0.5
Role limitations due to physical problems	6.41 (22.73)	4.31 (18.98)	0.6	10.71 (26.62)	4.84 (18.73)	0.3
Pain (SF 36)	19.66 (18.16)	17.06 (16.62)	0.5	22.28 (17.19)	15.96 (13.97)	0.1
General health	22.89 (11.66)	19.11 (14.97)	0.2	22.43 (12.5)	20.65 (12.14)	0.5
Vitality	16.71 (16.16)	9.66 (16.71)	0.06	14.24 (15.91)	13.71 (12.24)	0.8
Social functioning	40.13 (21.18)	34.82 (21.87)	0.3	41.42 (26.03)	34.67 (23.43)	0.2
Role limitations due to emotional problems	32.45 (44.84)	28.72 (40.55)	0.7	36.17 (40.71)	17.2 (37.38)	0.05
Mental health	40.42 (22.1)	37.93 (18.96)	0.6	42.3 (25.16)	36.26 (20.93)	0.3
Fatigue Severity Scale	6.36 (0.88)	6.51 (0.88)	0.4	6.2 (1.08)	6.64 (0.52)	0.04
Beck Anxiety Inventory	33.55 (12.35)	34.17 (13.2)	0.8	33.11 (13.22)	35.32 (12.77)	0.4
Pittsburgh Sleep Quality Index				13.84 (3.82)	14.25 (4.17)	0.6
McGill Pain Questionnaire	41.24 (8.45)	42.81 (8.01)	0.4	40.44 (10.21)	43.39 (8)	0.2
Pain Catastrophizing Scale	34.95 (12.08)	36.07 (11.41)	0.6	34.24 (14.09)	36.65 (12.53)	0.4
London Handicap Scale	58.52 (11.27)	57.27 (14.07)	0.6	60.12 (11.94)	55.36 (13.01)	0.1
Pain intensity (BPI)	7.01 (1.58)	7.06 (1.3)	0.8	6.87 (1.67)	6.91 (1.51)	0.9
Level of interference (BPI)	7.54 (1.61)	7.36 (1.74)	0.6	7.16 (1.82)	7.78 (1.61)	0.1
Myalgic score	5.21 (2.84)	3.8 (2.28)	0.02	3.94 (2.73)	2.66 (1.93)	0.02
Pressure pain threshold	79.47 (40.12)	65.8 (27.14)	0.09	79.25 (38.32)	56.71 (26.2)	0.004
Grip strength	79.51 (32.3)	83.38 (47.39)	0.6	78.25 (33.48)	77.34 (37.15)	0.9
Six-minute walk test	105.68 (97.94)	93.83 (80.38)	0.5	99.31 (92.62)	67.03 (74.42)	0.1
Subjective improvement	22.8 %	5 %	0.001			

BPI Brief Pain Inventory, *CAPG* capsaicin group, *CG* control group, *SF-36* short-form 36 health survey questionnaire, *VAS* Visual Analogue Scale

Analysis of clinical outcomes

At baseline (at week 0), there were no statistically significant differences in the baseline socio-demographic characteristics and the clinical outcomes between both groups (Table 1).

At the end of the intervention (at week 6), capsaicin-treated patients showed improvement in myalgic score (5.21 in capsaicin-treated versus 3.80 in controls, $p = 0.02$) and subjective improvement (16 cases in capsaicin-treated vs 3 cases in the control group, $p = 0.001$) (Table 2).

At the end of the follow-up (at week 12), 6 weeks after capsaicin discontinuation, those who have been treated with topical capsaicin still showed significant improvement in several clinical outcomes compared to controls (namely myalgic score, pressure pain threshold, FSS, FIQ, VAS of depression and role limitations due to emotional problems) (Table 2).

Discussion

There is an indirect evidence for a central dysfunction of the nociceptive modulating system in patients with FM. Some studies suggest that in these patients pain is associated with widespread primary and secondary cutaneous hyperalgesia, which are dynamically maintained by tonic impulse input from deep tissues and likely by brain-to-

spinal cord facilitation [19]. This conclusion is supported by results of several studies showing that injection of local anesthetics [20] into trigger points and muscles normalizes somatic hyperalgesia in FM patients. In this regard, several studies have found elevated CSF levels of SP [4].

Topically applied capsaicin induces the release of substance P. In addition, there is a specific blockade of transport and de novo synthesis of substance P. As a result, repeated applications of capsaicin lead to a long-lasting desensitization to pain for increase in pain threshold. The desensitizing effect is fully reversible. Capsaicin provokes a flare on the skin in FM patients, suggesting an increased activity of polymodal nociceptors. Also, capsaicin increases the area of secondary hyperalgesia [21].

Previous studies on the effect of topical capsaicin in patients with FM reached contradictory conclusions. In this regard, the first study assessed the efficacy of 0.025 % capsaicin cream four times daily in a 4-week, double-blind, vehicle-controlled study. Capsaicin-treated patients described a significant decrease in tender point tenderness and a significant increase in grip strength compared with control patients, but there were no statistically significant differences between groups in the Visual Analogue Scale for pain [22]. The second study followed a similar procedure, 0.025 % capsaicin cream, four times daily in a 4-week period in a series of 38 fibromyalgia patients [23]. Capsaicin-treated patients improved in the Visual Analogue Scale as well as in the number of tender points. However, 26.3 % of the patients did not experience any improvement. In both studies, the most common adverse effects attributable to capsaicin were transient burning and pricking at the application site, provoking in some cases discontinuation of treatment.

In our study, in patients receiving 0.075 % topical capsaicin, we did not observe significant differences in VAS of pain between capsaicin-treated patients and controls. Nevertheless, in our study several pain outcomes such as myalgic score and the pressure pain threshold improved significantly in capsaicin-treated patients compared to controls. Also, some other mood variables (VAS for depression and role limitations due to emotional problems) also improved, suggesting that the SP might play a relevant role in the pain well-being variables. Increased levels of intracerebral substance P have been associated with increased anxiety-like behavior in animals, and accordingly, NK1-receptor blockade with selective antagonist is associated with reduced stress and anxiety [24].

Finally, fatigue was also a health variable that improved in our study. As previously indicated [25], SP promotes release of some proinflammatory cytokines such us IL-1, IL-6 and TNF-α. IL-1 and TNF-α stimulate the release of NGF, and IL-1 promotes hyperalgesia, TNF-α allodynia and IL-6 fatigue and depression [25]. Therefore, it is possible that topical capsaicin might modulate the production of these mediators leading to clinical improvement.

Limitations of this study should be acknowledged. In this regard, the duration of treatment as well as the period of follow-up was relatively short. Due to this, additional studies aimed to establish that long-term efficacy of topical capsaicin should be conducted.

In conclusion, our study shows that patients severely affected by fibromyalgia can obtain short-term improvements following topical capsaicin 0.075 % treatment three times daily for 6 weeks.

Conflict of interest The authors declare that they have no conflict of interest.

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