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Role of heat therapy in the management of musculoskeletal pain

Contents

1. Musculoskeletal pain

a. Epidemiology

Pain related to musculoskeletal injury is one of the major causes of disability in industrialized countries. Back pain, including cervical and lumbar pain, is the most common form of musculoskeletal pain[1]. In Europe, low back pain is estimated to affect 12% to 39.2% of the adult population, with a lifetime prevalence between 60% and 85%[2]. According to the *Global Burden of Disease 2010 Study*, low back pain accounts for the largest number of years lived with disability among the approximately 300 conditions evaluated[3].

Pain related to musculoskeletal injury is one of the major causes of disability in industrialized countries.

b. Pathophysiology

Acute muscular injury may be caused by direct or indirect trauma[4]. In direct trauma, the resulting inflammation leads to edema, hyperalgesia and erythema, which may compound the muscular injury and delay healing[5]. Indirect muscular injury may be passive, due to excessive stretching of the muscle without contraction, or active, when the muscle undergoes excessive eccentric loading, which may lead to an acute injury or to delayed-onset muscle soreness (DOMS)[6,7].

The development of pain related to muscular injury derives from the activation of nociceptors present in the tissue, which convey the signal through the spinal cord to the brain, where it is recognised as painful. At the same time, neurotransmitters activate a spinal reflex that increases motor activity and tonicity at the site of injury, leading to a reflex muscle contraction. If increased muscle tone persists over time, it may cause painful muscle spasms, which in turn can exacerbate the tissue damage by reducing blood flow and oxygen supply to the area. This will lead to increased pain through a vicious circle (pain-spasm-pain) which must be interrupted to prevent the tissue damage and pain from becoming chronic[8].

In pain related to muscular injury, the vicious circle pain-spasm-pain must be interrupted to prevent the tissue damage and pain from becoming chronic.

c. Therapeutic approaches

Despite its high prevalence, musculoskeletal pain is undertreated[9]. The undertreatment of acute pain has important long-term consequences in that it can lead to acute pain becoming chronic[10]. Indeed, persistence of a severe acute pain causes prolonged neuroceptor activation, neuronal remodelling and the loss of inhibiting neurons, which in turn lead to secondary hyperalgesia and central sensitization of second-order spinal neurons[11].

Undertreatment can lead to acute pain becoming chronic through neuronal remodelling and the loss of inhibiting neurons.

The management of musculoskeletal injury includes both pharmacological and non-pharmacological approaches:

- Pharmacological therapies comprise non steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, muscle relaxants (for acute low back pain), antidepressants, corticosteroids (for back pain with radiculopathy) and opioids (for otherwise uncontrollable pain)[12]. Acetaminophen and ibuprofen, the most common over-the-counter medications, are generally considered the first-line treatment for acute low back pain even though their efficacy and safety have been questioned[13]. A systematic review has shown that these drugs do indeed have short-term efficacy in improving the symptoms of patients with acute low back pain, but they are associated with a high risk of renal, hepatic and gastrointestinal complications[14]. In addition, they often prove ineffective for

numerous patients[15] and have a risk of interaction with other ongoing treatments.

- Non-pharmacological therapies aim to reduce pain and the associated edema to promote the healing process, with no risk of side effects or pharmacological interactions: in this regard the use of heat therapy is a promising option.

Several pharmacological therapies for musculoskeletal pain exist; however, they are associated with a high risk of complications and they often prove to be ineffective.

2. Heat therapy: principles and applications

a. Rationale for the use of heat therapy in pain management

Heat therapy refers to the therapeutic application of any substance capable of transferring heat to the body, causing a rise in tissue temperature. Although the topical application of heat has been used therapeutically since antiquity, the pathophysiologic mechanisms underlying its efficacy are still not fully understood[8].

Heat causes a persistent vasodilatation[16], resulting in increased blood flow that facilitates the healing process by delivering proteins, nutrients and oxygen to the site of injury. A 1°C increase in tissue temperature is associated with a 10-15% increase in local tissue metabolism. This increase promotes healing by accelerating the catabolic and anabolic reactions necessary for removing the damaged tissue and promoting tissue repair[8].

Heat promotes healing by accelerating the local metabolic reactions.

At cell level, heat administration causes desensitization and a reduction of the activity of muscle spindles, with resulting muscle relaxation. Heat also causes a change in tissue viscosity and density, leading to increased plasticity of the muscle fibers and increased elasticity and extensibility of tissues[17].

Moreover heat acts by activating the heat receptors, nerve endings sensitive to heat, which transmit signals that block nociception at spinal cord level[8]. Neural heat transduction is mediated by TRP vanilloid 1 receptors (TRPV1), which are heat-activated ion channels. The TRPV1 receptors are located in primary afferent neurons of the spinal cord and brain. Their activation at brain level may modulate antinociceptive descending pathways, thereby contributing to the pain relieving action of heat therapy[1].

Some of the benefits of the topical application of heat might derive from a direct action at the level of the brain: heating of the skin surface seems able to activate some regions of the brain (thalamus and posterior insula), lessening the perception of pain and providing pain relief[8].

Therefore the overall efficacy of heat therapy derives from the increase in temperature induced in the tissues, which in turn alleviates pain, reduces muscle tone, increases blood flow and metabolism, and improves connective tissue extensibility[1].

The overall efficacy of heat therapy derives from the increase in temperature induced in the tissues, which in turn alleviates pain, reduces muscle tone, increases blood flow and metabolism, and improves connective tissue extensibility.

b. Evidence from the literature

The benefits of heat therapy for the management of acute and subacute low back pain were evaluated in a

Cochrane Review, comprising nine studies, for a total of over 1,000 patients. The analysis demonstrated the efficacy of heat therapy in the treatment of low back pain, in terms of reduced pain and disability[18].
The results of the main studies carried out to assess the efficacy of heat therapy for the management of low back pain are summarized in ***Table 1***.

A *Cochrane Review* demonstrated the efficacy of heat therapy in the treatment of low back pain, in terms of reduced pain and disability.

Table 1. Main evidence supporting the efficacy of heat therapy in the treatment of low back pain.

Study	Population	N	Design	Aim	Results	Comments
Nadler et al, 2003[19]	Patients (aged 18-55 years) with acute non-specific low back pain	219	Prospective, randomized, parallel, single-blind, placebo-controlled, multicenter clinical trial	To assess the efficacy of 8 hours of heat therapy (applied for approx. 8 hours on 3 consecutive days, with 2 days of follow-up) for the treatment of low back pain	Significantly greater efficacy of heat therapy vs placebo in terms of pain relief (day 1: $p<0.001$), less muscle stiffness (day 1: $p=0.008$), increased flexibility (day 1: $p=0.01$) and reduction of disability scores assessed with the Roland-Morris Disability Questionnaire (day 3: 5.3 vs 7.4; $p<0.0002$). No serious or significant adverse event associated with the use of heat therapy	Heat therapy proved to be more effective than placebo in decreasing pain, muscle stiffness and disability and in increasing flexibility in patients with non-specific acute low back pain
Nadler et al, 2003b[20]	Patients (aged 18-55 years) with acute non-specific low back pain	76	Prospective, randomized, parallel, single-blind, placebo-controlled, multicenter clinical trial	To assess the efficacy of 8 hours of heat therapy (applied for approx. 8 hours during the night, for 3 consecutive days, with 2 days of follow-up) for the treatment of low back pain	Significantly greater efficacy of overnight heat therapy vs placebo in terms of relieving pain throughout the next day ($p<0.001$) and for 2 days after treatment was completed ($p=0.00005$), improving morning stiffness ($p\leq0.02$ for all time points), trunk flexibility (day 4: $p<0.002$) and low back disability (day 4: $p=0.005$), and improving sleep quality	Overnight use of heat therapy reduced pain and disability for the 2 following days in patients with non-specific acute low back pain, and also improved sleep quality
Mayer et al, 2005[21]	Patients (aged 31.2±10.6 years) with low back pain of <3 months duration	100	Randomized controlled study	To assess the efficacy of heat therapy combined with physical exercise in the treatment of recent-onset low back pain	Significant improvement ($p<0.05$) in disability and pain 2 days after the last treatment compared with physical exercise alone or an educational intervention	Heat therapy combined with physical exercise proved more effective than exercise alone in reducing pain and disability in patients with recent-onset low back pain
Nadler et al, 2002[13]	Patients with acute non-specific low back pain	371	Prospective, randomized, single blind trial	To compare the efficacy of heat therapy (n=113) and acetaminophen (n=113) or ibuprofen (n=106) in terms of reducing pain, muscle stiffness and disability, and increasing trunk flexibility after 2 days of treatment and 2 days of follow-up	Significantly greater efficacy of heat therapy compared with ibuprofen or acetaminophen, in terms of pain relief and improved trunk flexibility at day 1 and following days (up to day 4), and reduced muscle stiffness on day 1 vs acetaminophen. Greater reduction in disability with heat therapy compared to pharmacological treatment, and good tolerability	Heat therapy proved to be more effective than pharmacological treatment in reducing pain, muscle stiffness and disability and increasing flexibility in patients with acute low back pain

A growing body of evidence indicates that heat therapy represents a valuable treatment option for the symptoms associated with low back pain and one that can be taken into consideration as an alternative to pharmacological therapy, as it allows early relief of symptoms and rapid return to normal activity[13,19-21].

As demonstrated by a systematic review of studies supporting non-pharmacological therapy for low back pain conducted by the American Pain Society/American College of Physicians, heat therapy represents the only intervention for which consistent evidence of efficacy is available[22].

A systematic review of studies supporting non-pharmacological therapy for low back pain showed that heat therapy represents the only intervention for which consistent evidence of efficacy is available.

Heat therapy (40°C for 8 hours for 3 days, with 2-5 days of follow-up) was also significantly more effective than acetaminophen in relieving pain, improving mobility and reducing disability in patients (n=89) with radiographically proven osteoarthritis associated with moderate pain[23].

Heat therapy showed efficacy also in osteoarthritis.

The therapeutic benefits of heat therapy have also been demonstrated in patients with wrist osteoarthritis, in whom a continuous local application of heat for 8 hours over 3 consecutive days resulted in progressively increasing pain relief that persisted to day 4-5 after the treatment was completed, compared to placebo[24].

Heat therapy proved efficacious also for the prevention and early treatment of DOMS: heat therapy initiated 4 hours before exercise (and applied for a total of 8 hours) was significantly more effective ($p<0.05$) than stretching in reducing pain intensity, self-reported disability and physical function impairments assessed 24 hours after exercise. Likewise, heat therapy applied (for 8 hours) 18 and 32 hours after exercise resulted in a significantly greater pain relief ($p=0.026$) compared to the application of cold packs[25].

Heat therapy applied before or after physical exercise showed efficacy in reducing DOMS (delayed onset muscle soreness).

The continuous application of heat therapy through a patch worn directly on the skin of the lower abdomen for 12 hours daily over 2 days by patients with dysmenorrhea resulted in a significantly greater pain relief compared with a control group not receiving heat therapy and similar to that obtained with the maximum dose of ibuprofen[26].

In patients with dysmenorrhea the continuous application of heat therapy resulted in a pain relief similar to that obtained with the maximum dose of ibuprofen.

c. Clinical use

Based on the available evidence, heat therapy can be used alone or in combination with oral analgesics to alleviate muscle pain in a variety of pathological conditions. Different American and European guidelines have long recognized the role of heat therapy in the management of musculoskeletal pain, recommending its use as a self-medication practice to manage acute low back pain[27,28]. The guidelines of the American College of Rheumatology recommend the use of heat therapy alone to reduce the pain and stiffness associated with hand osteoarthritis and the use of heat therapy combined with physical-therapist supervised exercise for the treatment of hip and knee osteoarthritis[29].

The main scientific guidelines have long recognized the role of heat therapy in the management of musculoskeletal pain.

Heat therapy must be used with caution in patients with diabetes, multiple sclerosis, circulation disorders, spinal cord injuries, and rheumatoid arthritis, as it can cause disease progression, increased inflammation, and skin burns or ulcers. In patients at high risk or with high sensitivity to heat, the skin should be protected before applying heat, especially in the presence of sensory impairments[1,8].

3. Calmadol®: evidence of efficacy and safety

Calmadol® is a self-heating device, available as a patch or a wrap and indicated for alleviating muscle tension, fatigue and cramping in the neck, shoulder and wrist regions and useful in the presence of arthritis-like pain and menstrual pain.

The device, which is medication-free and disposable, is made of non-woven fabric and has special cells containing substances such as iron powder, activated carbon and salt, which develop heat when entering into contact with the oxygen in the air.

a. Temperature monitoring

As demonstrated by laboratory tests (**Protocol 1608A12V**) conducted on healthy volunteers (n=7), the heat developed by the Calmadol® patch ensures maintenance of a skin temperature >40°C for almost 8 hours (480 min.) (***Figure 1***)[30].

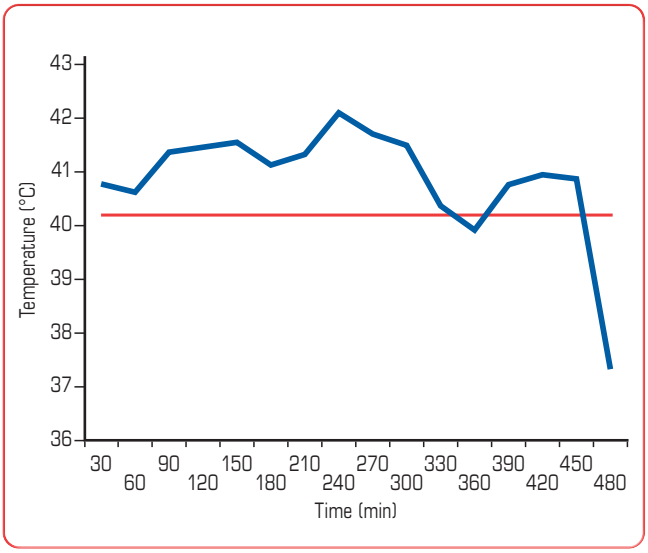

Figure 1. Stability of the temperature of the Calmadol® patch over 8 hours of use in healthy volunteers. Based on Eurosirel data[30].

The heat developed by the Calmadol® patch ensures maintenance of a skin temperature >40°C for almost 8 hours.

Similar results were obtained with the Calmadol® self-heating wrap, tested on 7 volunteers by applying the wrap to the skin and measuring skin temperature at 30-minute intervals for an overall period of 8 hours (480 min) (**Protocol 1608A14V**). The mean temperature measured over the 8-hour application period was 40.53°C (±0.45)[31].

The stability of the temperature obtained with Calmadol® was further evaluated in a pilot study (**Protocol 1804A15F**), carried out on 20 male and female patients (age range, 18-70 years) affected by joint and muscle pain. The study monitored the temperature (at 1-minute intervals for a total of 480 minutes) during the 8-hour application period and assessed skin tolerability (in terms of onset of edema or itching). The effect of the treatment on quality of life was evaluated through self-administered questionnaires in which patients were asked to rate personal satisfaction, subjective sensation of comfort, itching or pain on a scale from 0 to 10[32].

After an initial logarithmic growth, the temperature recorded during use remained constant over the 8-hour observation period, with mean values of 40-42°C (***Figure 2***)[32].

Skin tolerability, evaluated in terms of appearance of erythema or edema quantified on a scale from 0 to 4 (0=no erythema; 1=slight erythema; 2=clearly visible erythema; 3=moderate erythema; 4=severe erythema), after 8 hours of use of the medical device, showed a mean score of 1.2, with 1 in 4 patients not presenting any erythema, 1 in 3 with only slight erythema and the remaining patients with clearly visible erythema (***Figure 3***)[32].

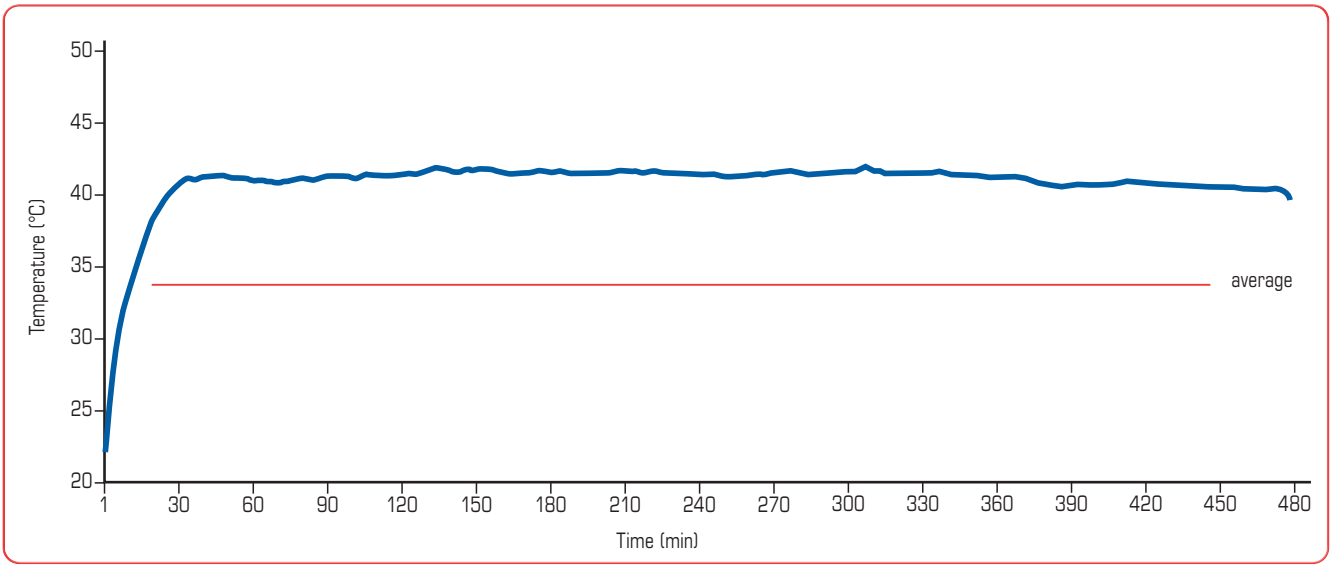

Figure 2. Monitoring of the temperature of the Calmadol® patch over 8 hours of use in patients with joint and muscle pain. Based on Eurosirel data[32].

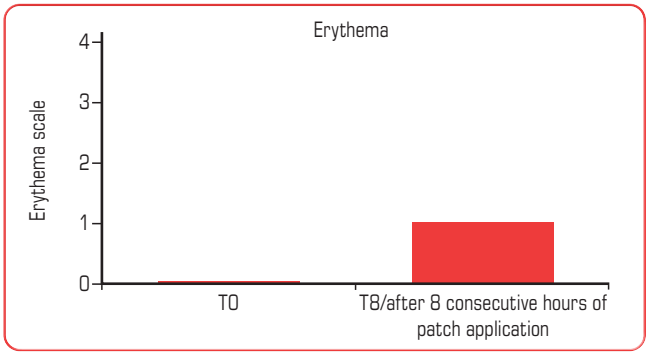

Figure 3. Mean score (obtained on a scale from 0 to 4) for the presence of erythema after 8 hours of Calmadol® use in patients with muscle pain. Based on Eurosirel data[32].

Tolerability of the device was also confirmed by the subjects' self-reported evaluations, which showed a mean score of 0.40 on a scale from 0 to 10 (0=not at all; 10=maximum), with only 2 in 20 patients reporting significant erythema (***Figure 4***)[32].

With regard to edema, the mean score after 8 hours of use was 0, with no patient developing visible edema.

The self-reported evaluations of efficacy (sensation of heat during use, sensation of relief, reduction in muscle tension) and ease/convenience of use showed mean scores >7, with an overall rating of the product and propensity to use it >8. In particular, the mean efficacy scores obtained for the sensation of relief and the sensation of reduced muscle tension (***Figure 5***) were equal to 7.60 and 7.85, respectively.

A minority of patients (n=3) reported the onset of burning or itching[32].

b. Clinical monitoring

The data collected during clinical monitoring of the safety and functionality of Calmadol® confirmed its efficacy in treating a variety of conditions characterized by musculoskeletal pain, arthritis-like pain and menstrual pain, in the absence of major side effects[33].

I. Muscle pain

A single-center study (**Protocol 1508F23F**) conducted on a group of 30 patients, male and female (aged 18 to 70 years), selected based on muscle tension, fatigue and cramping, aimed to confirm the efficacy of the treatment in relieving the pain associated with these conditions and in promoting relaxation and hence mobility of the affected area. The study also assessed the tolerability of the device by monitoring the onset of side effects (erythema and/or edema), as well as improvements in quality of life (reduction of discomfort and increase in performance) associated with improved mobility and reduced muscle tension and fatigue. All parameters were assessed by patients on a scale from 0 to 10 (0=not at all; 10=maximum)[33].

Vol. Ref.	Score
1	0
2	1
3	1
4	0
5	0
6	3
7	0
8	0
9	0
10	0
11	0
12	0
13	0
14	0
15	0
16	0
17	0
18	0
19	3
20	0
Average	**0.40**

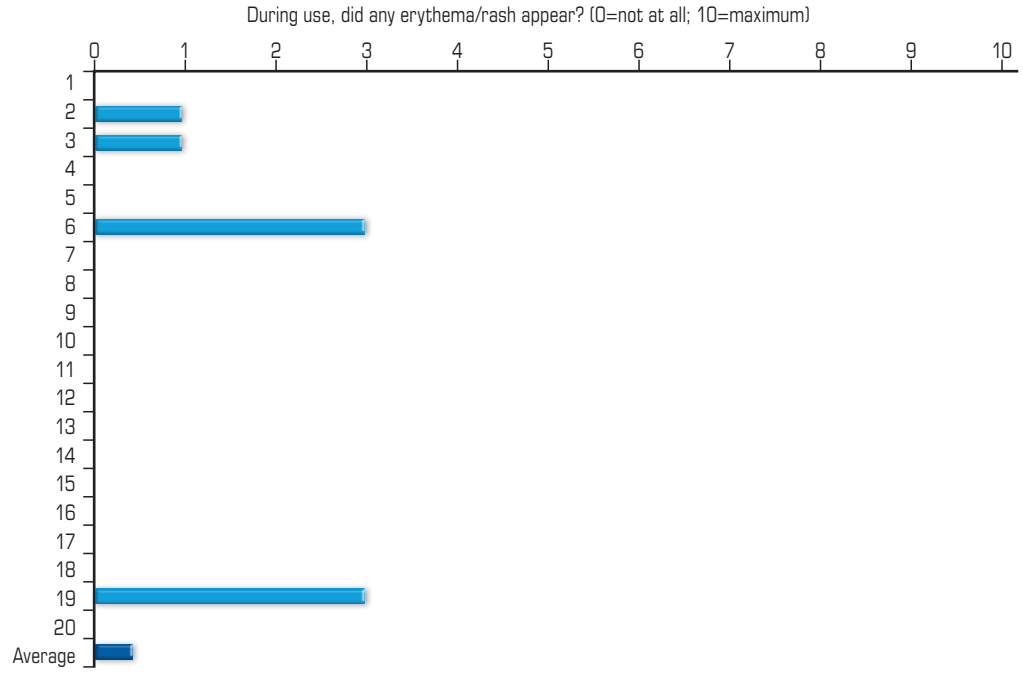

Figure 4. Scores (obtained through self-reported ratings on a scale from 0 to 10) for the presence of erythema after 8 hours of Calmadol® use in patients with muscle pain. Vol. Ref.=volunteer reference. Based on Eurosirel data[32].

Vol. Ref.	Score
1	8
2	5
3	6
4	8
5	8
6	8
7	10
8	9
9	8
10	7
11	9
12	8
13	8
14	8
15	7
16	9
17	8
18	5
19	8
20	10
Average	**7.85**

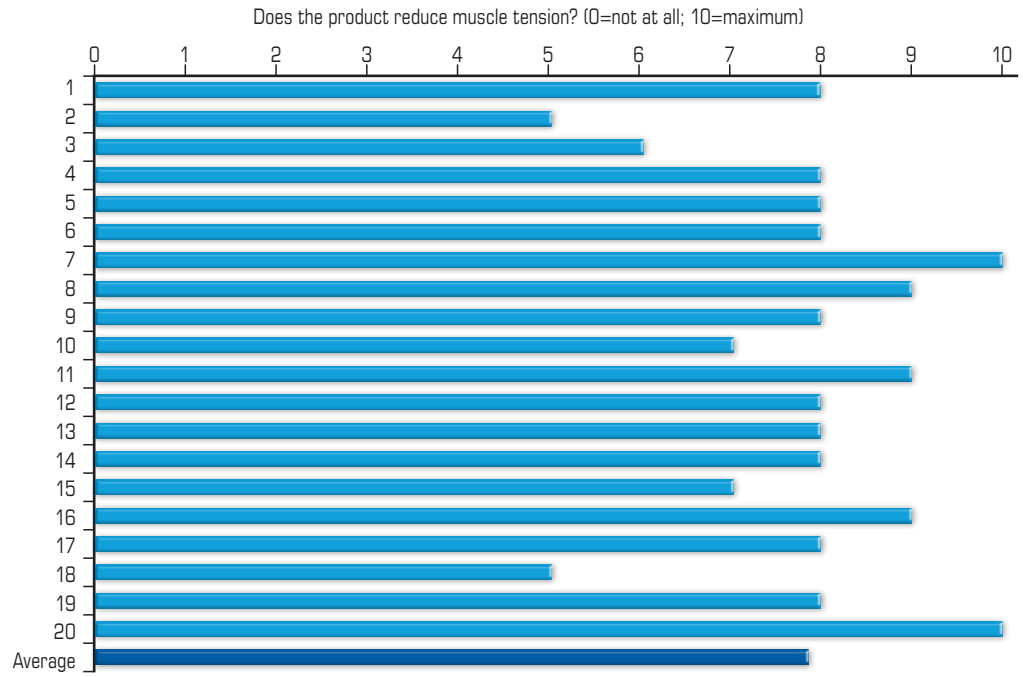

Figure 5. Score (obtained through self-reported ratings on a scale from 0 to 10) for the reduction of muscle tension after 8 hours of Calmadol® use in patients with muscle pain. Vol. Ref.=volunteer reference. Based on Eurosirel data[32].

All of the parameters considered for evaluating the efficacy of the device (sensation of warmth during use, sensation of warmth persisting for 8 hours, sensation of relief during use, sensation of relief persisting after re-

moval, reduced muscle tension, improved mobility) received an overall mean rating ≥8 (***Figure 6***)[33].

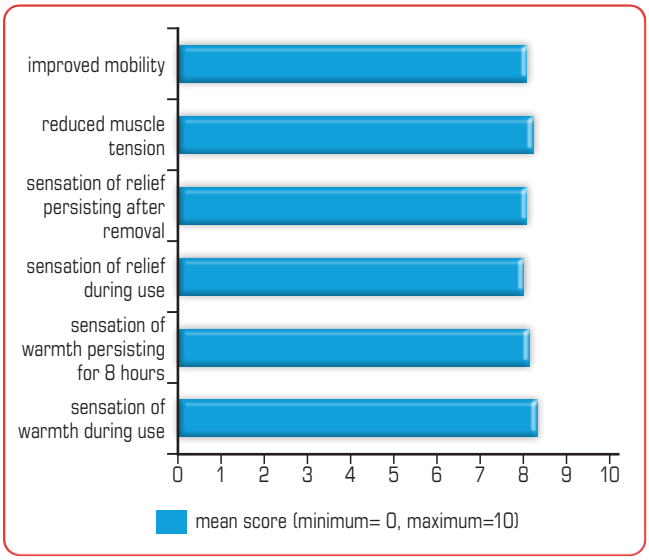

Figure 6. Cumulative results of the patients' self-reported evaluations of the efficacy of Calmadol® for muscle pain. All parameters were rated on a scale from 0 to 10. Based on Eurosirel data[33].

Similarly, all the parameters considered for evaluating the ease and convenience of use of the device also obtained high scores (9.1 and 8.8, respectively), giving rise to an extremely positive overall rating of the device and propensity to buy it based on its characteristics (8.6 and 8.7, respectively) (***Figure 7***)[33].

As for the evaluation of tolerability, no skin changes (erythema or edema) were reported by any of the subjects tested (Eurosirel data[33]).

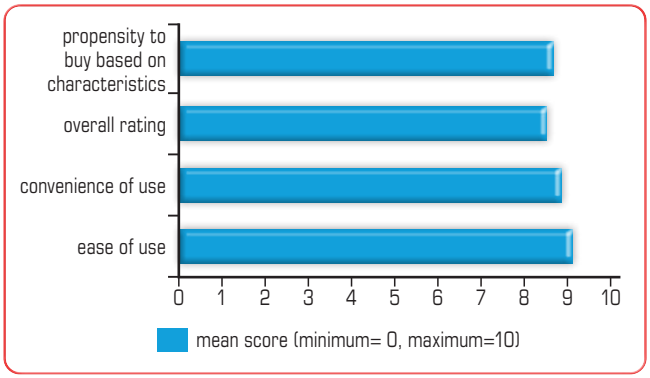

Figure 7. Overall results of patients' self-reported evaluation of the ease and convenience of use of Calmadol® for muscle pain. All parameters were rated on a scale from 0 to 10. Based on Eurosirel data[33].

In muscle pain, Calmadol® showed a good tolerability, ensured a sensation of relief, showed ease and convenience of use.

II. Arthritis-like pain and menstrual pain

A single-center study (**Protocol 1508L21F**) was conducted on a group of 30 males and females (aged 18 to 70 years), affected by arthritis-like pain or menstrual pain, subdivided into two groups of 15 subjects each (Group 1: 15 men and women with arthritis-like pain; group 2: 15 women with menstrual pain). The aim of the study was to confirm the efficacy of Calmadol® treatment in alleviating arthritis-like pain and menstrual pain, and to assess its ability to promote relaxation of the affected region. The study also evaluated skin tolerability (in terms of erythema and/or edema) of the device and the improvement in quality of life (reduction of discomfort and increase in performance) associated with reduced muscle tension. All the parameters were rated by the patients on a scale from 0 to 10 (0=not at all; 10=maximum)[34].

All the parameters considered for evaluating the efficacy of the device (sensation of warmth during use, sensation of warmth persisting for 8 hours, sensation of relief during use) received an overall average rating ≥7. As regards the sensation of pain relief during use, evaluated separately according to the origin of the pain, the score was slightly lower for patients with menstrual pain (6.87) compared to those with arthritis-like pain (7.2) (***Figure 8***)[34].

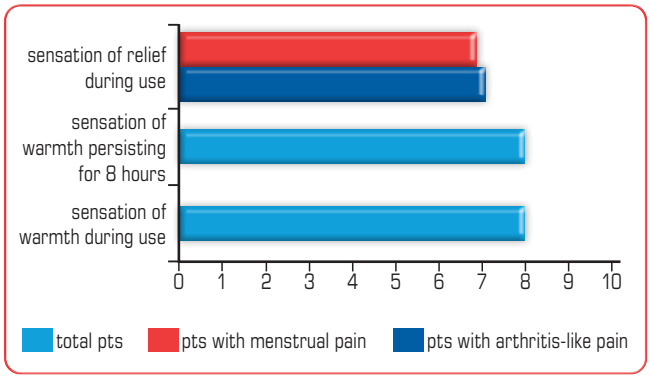

Figure 8. Cumulative results of patients' self-reported evaluation of the efficacy of Calmadol® in arthritis-like pain or menstrual pain. All parameters were rated on a scale from 0 to 10. pts=patients. Based on Eurosirel data[34].

The parameters considered for the evaluation of ease and convenience of use obtained higher scores (8.57 and 8.6, respectively), leading to a generally positive rating of the device and of the patient's propensity to buy it based on its characteristics (7.63 and 7.70, respectively) (***Figure 9***)[34].

As for the evaluation of tolerability, no skin changes (erythema or edema) were reported by any of the subjects[34].

In patients with arthritis-like pain or menstrual pain Calmadol® use was associated with pain relief and improved quality of life.

The efficacy and tolerability results obtained with Calmadol® by the reported studies are summarized in ***Table 2***.

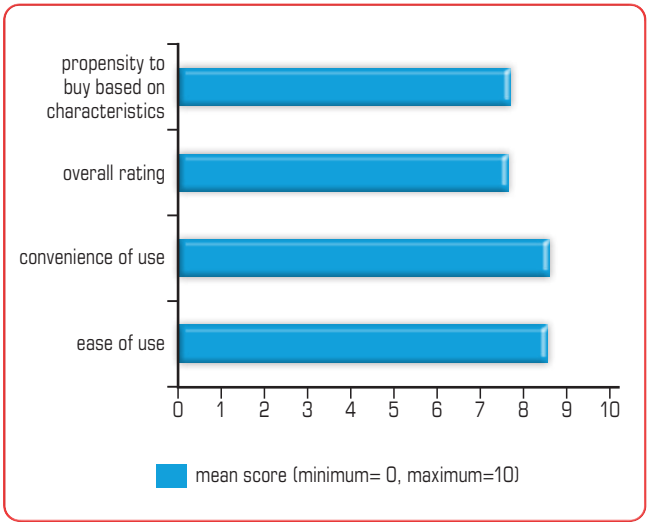

Figure 9. Cumulative results of patients' self-reported evaluation of ease and convenience of use of Calmadol® in arthritis-like pain or menstrual pain. All parameters were rated on a scale from 0 to 10. Based on Eurosirel data[34].

Table 2. Main evidence supporting the efficacy and tolerability of Calmadol® in the treatment of musculoskeletal pain

Protocol	Device tested	Population	N	Efficacy endpoint	Tolerability endpoint	Efficacy results	Tolerability results
1608A12V[30]	Calmadol® self-heating patch	Healthy subjects	7	Assessed stability of temperature developed		Skin temperature >40°C for almost 8 hours	
1608A14V[31]	Calmadol® self-heating wrap	Healthy subjects	7	Assessed stability of temperature developed		Mean skin temperature 40.53°C (±0.45) over 8 hours of use	
1804A15F[32]	Calmadol® self-heating patch and wrap	Patients with joint and muscle pain	20	Assessed stability of temperature developed; Assessed effect on quality of life	Assessed skin tolerability	Mean skin temperature between 40°C and 42°C over 8 hours of use. Mean efficacy scores (from self-reported ratings on a scale from 0 to 10): Sensation of relief: 7.60 Reduction in muscle tension: 7.85	Mean score for erythema onset (assessed on a 5-point scale): 1.2. Mean score for erythema onset (from self-reported ratings on a scale from 0 to 10): 0.40. No edema
1508F23F[33]	Calmadol® self-heating patch and wrap	Patients with muscle tension, fatigue and cramping	30	Assessed efficacy in relieving pain, promoting relaxation of affected area and improving mobility; Assessed effect on quality of life	Assessed skin tolerability	Mean overall scores (from self-reported ratings on a scale from 0 to 10) for efficacy parameters (sensation of warmth during use, sensation of warmth persisting for 8 hours, sensation of pain relief during use, sensation of pain relief persisting after removal, reduction in muscle tension, improvement in mobility): ≥8; Mean scores for ease of use, convenience of use, propensity to buy and overall rating between 8.6 and 9.1	No skin change (erythema or edema) in any of the subjects

Protocol	Device tested	Population	N	Efficacy endpoint	Tolerability endpoint	Efficacy results	Tolerability results
1508L21F[34]	Calmadol® self-heating patch and wrap	Patients with arthritis-like pain or menstrual pain	30	Confirmed efficacy of Calmadol® in alleviating arthritis-like pain and menstrual pain, and assessed the ability of the device to promote relaxation of affected area; Assessed the efficacy of Calmadol® in improving quality of life (reduction of discomfort and increase in performance) associated with reduced muscle tension	Assessed skin tolerability (in terms of onset of erythema and/or edema)	Mean overall scores (from self-reported ratings on a scale from 0 to 10) for efficacy parameters (sensation of heat during use, sensation of heat persisting for 8 hours, sensation of pain relief during use): ≥7; Mean scores for ease of use, convenience of use, propensity to buy and overall rating between 7.63 and 8.6	No skin change (erythema or edema) in any of the subjects

4. Calmadol®: practical information[35]

Indications

The Calmadol® self-heating patch and wrap are indicated for the treatment of muscle and joint pain. Both devices relieve muscle tension, fatigue or cramping by providing constant therapeutic heat for a period of 8 hours. Both can also prove useful for treating menstrual pain. The self-heating Calmadol® patch can be used on any part of the body; the self-heating Calmadol® wrap is indicated for use on the neck, back and wrist.

Instructions

Before applying the wraps or patches, clean and thoroughly dry the affected area. Place the patch/wrap on the area making sure the whole surface of the patch/wrap adheres to the skin, and keep it on for at least 8 hours. If using the patch for period pains, place it with the adhesive surface towards your underwear and not directly on the skin. Make sure it adheres perfectly.

Warnings and contraindications

Discontinue use in the case of:

- discomfort, irritation, excessive sensation of heat, burning, swelling, redness or any other skin change in the area where the product has been placed;
- failure to solve the problem for which the product has been used.

Do not use in the case of:

- concomitant use of creams, ointments or other heat products;
- broken skin;
- bruising or swelling in the past 48 hours;
- leakage from the heating cells and/or damaged product.

If you suffer from circulatory problems, heart disease or rheumatoid arthritis, or if you are pregnant, you should seek your doctor's advice before using the product (Calmadol®, https://montefarmaco.com).

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