

Drug Corner

Clinical Effectiveness and Tolerability of 2% Menthol in Musculoskeletal Pain : A Pilot Observational Real-world Evidence Study

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Objective : To determine the efficacy and safety of 2% menthol in the management of musculoskeletal pain.

Materials and Methods : 81 patients above the age of 18 years of either sex with any musculoskeletal pain were included in the study. Subjects were instructed to apply 2% menthol gel twice daily to the affected area for 7 to 10 days. A Visual Analog Scale (VAS) was used to assess the severity of the initial pain. Moreover, the level of muscle soreness on a 7-point Likert scale was also evaluated. The patients were assessed before the treatment and 7 to 10 days after the initiation of the treatment.

Results : The VAS scores for pain significantly improved ($P < 0.0001$) in subjects after completion of the treatment. There was a 70% improvement (7.67 ± 1.04 before treatment to 2.30 ± 0.56 after treatment) in the VAS scores compared to baseline, and the mean Likert scale of muscle soreness was 2.04 ± 0.25 at the end of the treatment. Moreover, no significant adverse events were observed in the patients during the study.

Conclusion : The study showed that 2% menthol effectively improves musculoskeletal pain.

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Key words : Musculoskeletal Pain, Muscle Pain, Menthol.

Musculoskeletal pain is the acute or chronic discomfort that impacts various body parts, including bones, muscles, tendons, ligaments, and even nerves. Musculoskeletal pain is the leading cause of disability in people in their working years. It is characterized by the mild, moderate, or severe muscle discomfort, soreness, or stiffness in the muscles. The World Health Organization reports that around 1.75 billion people worldwide, equivalent to 20-33% of the global population, are affected by chronic musculoskeletal pain in varying degrees¹. Muscle pain can be caused by various factors, including injury, overuse, infection, inflammation, or certain medical conditions². Sometimes, the pain may be accompanied by swelling, redness, or warmth in the affected area. Individuals with muscle pain may also experience fatigue, weakness, or difficulty moving the affected muscle or joint³. Injuries to the muscle, such as strains or sprains, can result from overuse, trauma, or excessive stretching. Chronic low back pain, neck pain, and the pain linked to osteoarthritis and rheumatoid arthritis are the most commonly occurring types of musculoskeletal pain. Still, musculoskeletal

pain also includes sprained muscles, pain associated with fractures, shoulder pain, and others⁴. Muscle pain is commonly managed pharmacologically with analgesics, particularly Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), to preserve the patient's ability to complete functional tasks⁵. Each major type of analgesic drug (NSAIDs like ibuprofen, aspirin, naproxen, and opioids such as codeine, oxycodone, and hydrocodone) is associated with adverse effects or abuse potential limitations. Thus, there is interest in discovering new agents that produce pain relief by alternative mechanistic pathways. Non-toxic therapies are needed to reduce pain with minimal side effects⁶.

Menthol has been used as a topical pain reliever since ancient times. Menthol (also known as mint camphor) is found as a significant constituent in the essential oils of *Mentha canadensis* L. (cornmint) and *M. x piperita* L. (peppermint). Menthol is recognized for its capability to induce sensations of coldness, and in addition, it possesses properties that can alleviate pain and irritation. Applied to the skin, it imparts a cooling effect and might act as a weak sodium channel blocker^{7,8}. Its action on activity-dependent voltage-gated neuron channels confers a weak, localized anaesthetic effect. Studies have demonstrated that voltage-gated Na⁺ channels play a crucial role in the perception of pain. Menthol produces cooling sensations by stimulating cold receptors, which is achieved by inhibiting Ca²⁺ currents in neuronal

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membranes. Additionally, menthol induces a sensation of coldness by activating ion channels belonging to the Transient Receptor Potential (TRP) family. TRPs are distributed throughout the body, but TRPM8 is predominantly present in thermosensitive neurons, which respond to decreases in temperature and are also activated by menthol. TRPM8 serves as a neuronal sensor of cold temperatures and is essential for innocuous cool and noxious cold sensations^{9,10}. Activation of these thermosensitive neurons is also linked to the pain-relieving effect of menthol-based topical gels¹¹. Menthol has been documented to possess various biological properties through in vitro and in vivo studies, including its ability to act as an analgesic, anaesthetic, and penetration enhancer¹². The purpose of the study is to check the safety and effectiveness of 2% mentholgel in managing musculoskeletal pain.

MATERIALS AND METHODS

Study Design :

The present study was designed as a Pilot Observational Real-world evidence study involving patients with musculoskeletal pain. The study protocol and related materials were approved at Grecian Superspeciality hospital, Mohali (RGS/CC/CM-17/8/2022) and were in compliance with ICMR (Indian Council of Medical Research), New Drugs and Clinical Trials Rules, 2019, ICH GCP, and the declaration of Helsinki. Before the start of the study, written consent was obtained from all participants.

Setting and Participants :

81 patients above the age of 18 years of either sex with any musculoskeletal pain were included in the study. Patients with musculoskeletal injuries, pregnant and lactating women, allergic or hypersensitive to menthol, and unable to understand the procedures and protocol were excluded from the study.

Study Intervention :

During the study, the subjects were instructed to apply 2% menthol gel

twice daily for at least 7 to 10 days. Universal NutriScience Pvt Ltd, Mumbai, marketed the formulation. The record of concomitant medications, if any, was maintained during the study.

Outcome Measures :

The subjects rated the pain on a 10-mm visual analog scale (VAS). The subjects rated the level of muscle soreness on a 7-point Likert scale. The VAS score for pain was evaluated at the start and end of the treatment with 2% menthol.

Statistical Analysis :

A primary database was created in validated Microsoft Excel spreadsheets while processing case record forms received from the study sites. The data were analyzed using an unpaired Student T test, with a P-value < 0.05 considered statistically significant. The final manuscript described and substantiated all deviations from the final version of the statistical analysis plan.

RESULTS

Patient Demographics :

A total of 81 patients were enrolled during the study based on inclusion and exclusion criteria, comprising 47 (58.02%) males and 34 (41.98%) females. The mean age of subjects was 49.9 years. All the subjects selected during the study applied 2% menthol gel at the affected site twice daily for up to 10 days. Intake of NSAIDs was observed in 6 patients (7.41%). Fig 1 depicts the symptoms of musculoskeletal pain (pain, stiffness, swelling and soreness) experienced by the patients before starting the treatment.

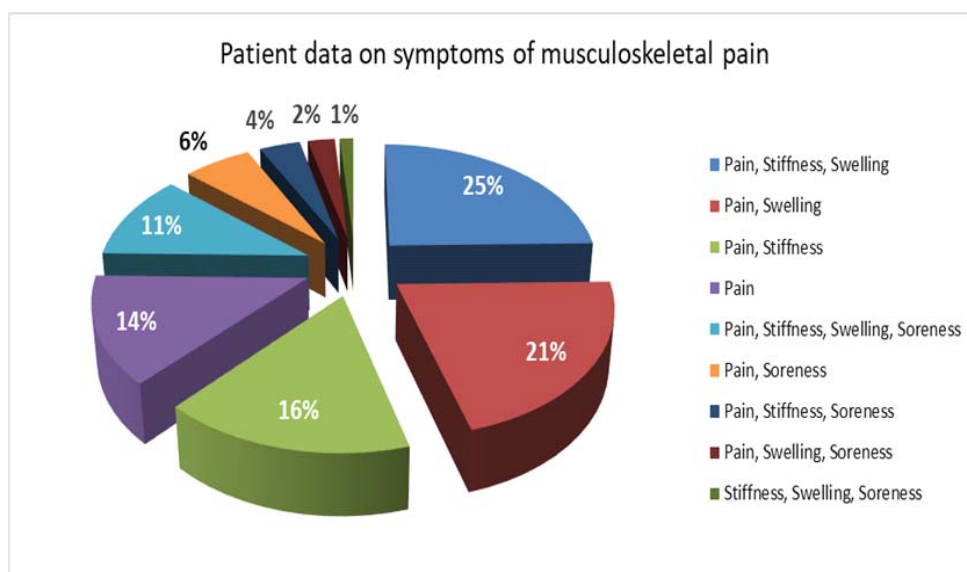


Fig 1 — Patient data on symptoms of musculoskeletal pain

VAS Score :

There was a significant improvement ($P < 0.0001$) in the VAS scores for pain at the end of the treatment period when compared to baseline (day 0). At the baseline, the mean VAS score was 7.67 ± 1.04 , which improved significantly to 2.30 ± 0.56 at the end of treatment, with a percent improvement of 70%, as depicted in Fig 2.

Likert Scale of Muscle Soreness :

The mean Likert scale of muscle soreness score was observed to be 2.04 ± 0.25 at the end of the treatment with 2% menthol. Table 1 describes the percentage of subjects experiencing muscle soreness using the Likert scale of muscle soreness after treatment.

Safety :

There were no adverse events observed in the patients during the study.

DISCUSSION

Musculoskeletal pain can be difficult for patients and healthcare providers to manage. It is a common experience among adults, regardless of factors such as age, gender, or economic status. Inadequately managed musculoskeletal pain can adversely affect the quality of life^{13,14}. This Pilot Observational Real-world evidence study investigated the effectiveness of 2% menthol gel in managing musculoskeletal pain. There was a significant improvement of 70% in the VAS scores for pain at the end of treatment. The findings from the present study are consistent with previous research that investigated the effects of topical menthol at various concentrations on individuals with muscle or joint pain. A study conducted by Topp, *et al* indicated that topical menthol 3.5% intervention significantly reduced pain by around 27-37% during the different functional tests and improved functioning among knee osteoarthritis patients¹⁵. Another study conducted by Fallon *et al*. demonstrated that 82% of subjects with neuropathic pain had an improvement in total Brief Pain Inventory scores after treatment with topical 1% menthol cream twice daily¹⁶. The decline in pain during the treatment period of 7-10 days in our study and other studies appears to be highly clinically significant following the application of menthol treatment. The limitation of this study is the relatively small sample size and a single-arm open study, which may limit the generalizability of the findings to a larger population. However, the

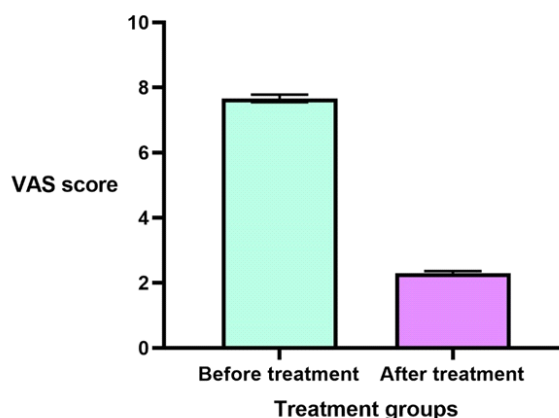


Fig 2 — Change in the VAS scores before and after the treatment

Table 1 — Percentage of subjects experiencing muscle soreness using the Likert scale of muscle soreness after treatment

Observations	Subjects experiencing the symptoms	Subjects not experiencing the symptoms
Complete absence of soreness	3.70 %	96.30 %
Light pain felt only when touched	83.95 %	16.05 %
Moderate pain felt only when touched	16.05 %	83.95 %
Light pain while walking / other activities	75.31 %	24.69 %
Mild pain while walking / other activities	18.52 %	81.48 %
Moderate pain while walking / other activities	4.94 %	95.06 %
Severe pain that limits the ability to move	1.23 %	98.77 %

results of this study support the suggested analgesic mechanism of menthol and agree with similar studies that have been conducted. This consistent evidence regarding the effectiveness of topical menthol in relieving pain provides the clinician with another approach to treating musculoskeletal pain among patients. Using topical menthol as a stand alone therapy or as a complement to standard pharmacological pain therapy may enhance pain relief.

CONCLUSION

These preliminary findings appear to support the efficacy of a 2% menthol gel in musculoskeletal pain.

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Conflict of interest : The authors declare no conflict of interest.

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