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Efficacy of Cold Gel for Soft Tissue Injuries

A Prospective Randomized Double-Blinded Trial

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Background: The use of cold treatment to limit edema, decrease pain, and induce effective muscle relaxation in soft tissue injuries is widespread.
Purpose: To compare the efficacy of a novel cold gel with that of a placebo gel in patients with a soft tissue injury.
Study Design: Prospective randomized double-blinded controlled study.
Methods: Seventy-four patients with sports-related soft tissue injury were randomly assigned to active cold gel (Ice Power) or placebo gel groups. The gel was applied four times daily on the skin for 14 days. Clinical assessment was made after 7, 14, and 28 days with use of visual analog scale ratings.
Results: Pain scores decreased from 59 to 30 during the first week, to 14 by the second, and to 7 by the end of study in the cold gel group. In the placebo group, pain scores decreased from 58 to 45, 26, and 13, respectively (significant difference). Patient satisfaction with treatment was 71 in the cold gel group and 44 in the placebo group (significant difference). Disability decreased significantly more rapidly in the cold gel group.
Conclusions: Cold gel therapy provided an effective and safe treatment for sports-related soft tissue injuries.

The use of cryotherapy is widespread in sports medicine today. The application of cold is a popular and established method for treating acute soft tissue injuries, but there is a discrepancy between the scientific basis for cryotherapy and actual clinical studies. Various cooling procedures have been used to apply cold to the injured area, such as ice packs, ice towels, ice massage, frozen gel packs, ethyl chloride and other vapor coolants, chemical reaction devices, and inflatable splints that use refrigerant gas.[3,13,19,21]

Most clinical studies of the use of cryotherapy for various injuries have shown a positive effect on pain relief and on recovery.[3] Cryotherapy, if started within 36 hours after the injury and used for a minimum of 3 days, was statistically more effective than heat therapy for complete and rapid recovery of acute ankle sprains.[11] Cold is also used to reduce recovery time as part of the rehabilitation program for the treatment of both acute and chronic injuries. Cryotherapy has also been shown to effectively reduce pain in the postoperative period after reconstructive surgery of the joints.

The physiologic and biologic effects of cryotherapy are due to the reduction in temperature in the various tissues, together with neuromuscular actions and relaxation of the muscles.[16,17] Both superficial and deep temperature changes depend on the method of application, the initial temperature, and the application time.[3,13,17,19,20]

Cold therapy appears to be effective and harmless, and few complications or side effects have been reported after its use. Prolonged application at very low temperatures should, however, be avoided, as this may cause serious side effects, such as frostbite and nerve injuries.[6,7] Practical applications, indications, and contraindications are poorly known, and randomized clinical trials have not been performed on the efficacy of cold therapy for patients with soft tissue injuries.

A novel cold-producing cream (gel), with ethanol and menthol as the active cold-forming agents, has been developed for cold application to an injured area. The aim of our trial with this novel cold-mediating gel was to study

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its efficacy to relieve pain and to decrease functional disability. We also evaluated its safety in a randomized controlled study design of patients with acute sports-related soft tissue injuries, comparing the active cold gel with a placebo gel.

PATIENTS AND METHODS

The study population consisted of 74 patients with sports-related soft tissue injury of the ankle, leg, knee, or hand. The patients were randomly assigned to active cold gel (Ice Power, Fysioline Ltd., Tampere, Finland) (13 women and 24 men with a mean age of 32 ± 12 years) or placebo gel (14 women and 23 men with a mean age of 32 ± 10 years) groups (Table 1).

Patients were included in this study after a careful clinical evaluation that included a history and physical examination. The movement restrictions and pain at palpation and movement during the examination were recorded with use of a three-category scale (none, mild, severe). Edema of the injured area was also graded on a three-category scale (none, mild, severe) by clinical inspection and palpation. Only patients with minor soft tissue injury of the extremities that had occurred less than 48 hours before the examination were included. Exclusion criteria were as follows: pain on the visual analog scale of less than 30 mm, pregnancy, the presence of cutaneous lesions or injuries at the site of application that would prevent the use of gel therapy, and an injury needing surgery or physiotherapy. The use of nonsteroidal antiinflammatory drugs was allowed in both groups as a rescue medication, and any use was recorded. Injuries were classified into three groups according to severity. The location of injuries is shown in Table 2. All patients with knee or ankle injuries used elastic bandages (Beiersdorf AG, Hamburg, Germany) for 14 days.

The study design was prospective, randomized, and double-blinded. The randomization was made in groups of four, taking into account the sex, injury type, and age, by a computer program designed to reach an equal comparison of groups. The randomization program was kept separately from the investigators and only opened after all patients had attended the final follow-up visit.

This study was approved by the Ethical Committee of Kuopio University Hospital. All patients were informed that they were participating in a clinical study in which their soft tissue injuries would be treated randomly with use of one of two different gels, one including active agents and the other a placebo. The patients were not informed of the sensations they would feel nor were the effects of cold discussed.

The cold gel group applied 5 g of Ice Power four times a day for 14 days on the painful injured area. The placebo group received the same treatment with a placebo gel. Patients in both groups were given identical instructions on the use of the gels. The gel was applied onto the skin with use of the fingers to apply a slight massage. The active cold gel consisted of 3.5% menthol and 8% ethanol and adjuvants. The placebo gel was made similarly but without ethanol and menthol. The gel tubes, which consisted of 250 g of gel at the beginning of the study, were returned after 14 days and the amount of gel used was recorded. Only 15 patients reported using nonsteroidal antiinflammatory drugs during the evaluation time (Table 3). Only one patient in the placebo group had dropped out by the final visit on the 28th day.

The follow-up visits were scheduled at 7, 14, and 28 days. Clinical evaluations were made at every visit. The primary end points of the study were pain at rest, pain on movement during normal function, and functional disability. The secondary end points were the patient's and investigator's global assessment and satisfaction with the treatment and the patient's readiness to use the same treatment, if she or he had a similar injury. All of these outcomes were measured on visual analog scales with scores expressed as millimeters from 0 to 100.[18] In addition, the global assessment of the therapy and the patient's satisfaction were also measured by use of a questionnaire, in which the choices were the following: 0, no benefit or harm; 1, little benefit; 2, good benefit; and 3, excellent benefit.[1] At the last visit, the patients were asked an open question regarding their feelings about the study and about improvements in the symptoms of their soft tissue injury.

All results were expressed as the mean ± SD. The clinical outcome variables were analyzed on the basis of

TABLE 1
Patient Characteristics

Characteristic	Placebo group	Cold gel group
Women	14	13
Men	23	24
Mean age of all subjects (years)	32 ± 10	32 ± 12
Mean age of women (years)	34 ± 9	35 ± 9
Mean age of men (years)	31 ± 10	30 ± 13
Mean height of all subjects (cm)	178 ± 11	177 ± 12
Mean weight of all subjects (kg)	77 ± 11	76 ± 11

TABLE 2
Locations of Injuries by Treatment Group

Location	Placebo gel group	Cold gel group
Foot	4	3
Ankle	12	11
Knee	9	10
Wrist	7	6
Hand	1	2
Other location	4	5
Total injuries	37	37

TABLE 3
Use of Nonsteroidal Antiinflammatory Drugs

Drug	Placebo group	Cold gel group
Ibuprofen	4	3
Nimesulide	3	3
Diclofenac	2	0

intent to treat. Statistical comparison between the groups was made by using a two-way Student's *t*-test, the Mann-Whitney *U*-test, and analysis of variance. Bonferroni correction was used for correction of the significance levels for multiple testing. The statistical significance was set at $P < 0.05$.

RESULTS

The pain experienced by patients in both the placebo and cold gel groups was at the same level at the beginning of this study. During the trial, pain decreased markedly in both the cold gel and placebo groups as measured on a visual analog scale at each measuring time both at rest and on movement. The differences between the groups were highly significant (Figs. 1 and 2).

The pain at rest decreased from 59 ± 15 to 30 ± 16 during the 1st week, to 14 ± 13 at 14 days, and to 7 ± 12 at 28 days in the active cold gel group. In the placebo group, the pain at rest decreased from 59 ± 15 to 45 ± 15, 26 ± 18, and 13 ± 14, respectively ($P < 0.001$) (Fig. 1).

The pain on movement decreased from 57 ± 14 to 27 ± 13 during the 1st week, to 13 ± 12 at 14 days, and to 6 ± 11 at 28 days in the active cold gel group. In the placebo group, the pain on movement decreased from 59 ± 15 to 41 ± 14, 21 ± 13, and 13 ± 12, respectively ($P < 0001$) (Fig. 2).

The functional disability evaluated by the visual analog scale was 63 in the cold gel group and 62 in the placebo group at the beginning of the study. The score decreased to 31 at 7 days in the active cold gel group but to only 48 in the placebo group ($P < 0.001$). The improvement was statistically highly significant in the active cold gel group compared with the placebo gel group at each follow-up visit (Fig. 3).

The patients' satisfaction with the treatment as assessed by the visual analog scale was 71 in the active cold gel group and 44 in the placebo group ($P < 0.001$).

The patients' global assessment of the treatment (score from 0 to 3) at the end of the study was significantly favorable for the active cold gel treatment (2.3 ± 0.3 for cold gel versus 1.4 ± 0.3 for placebo, $P < 0.001$). The investigator's assessment (score from 0 to 3) also favored the active cold gel treatment (2.4 ± 0.3 for cold gel versus 1.5 ± 0.3 placebo, $P < 0.001$).

Two patients in each group reported minor skin abrasion after the application of the gel onto the skin. None of these patient felt sufficient discomfort to discontinue the study. No other adverse events were reported during the study.

Five patients in the placebo gel group assumed that they had been assigned to use of the placebo gel, whereas no one in the cold gel group thought that they were using a placebo. The patients returned the gel tubes to the investigator after the 14th day for evaluation of the amount of gel used. The mean amount of gel used was 224 ± 16 g in the cold gel group and 196 ± 17 g in the placebo gel group; the difference was not significant.

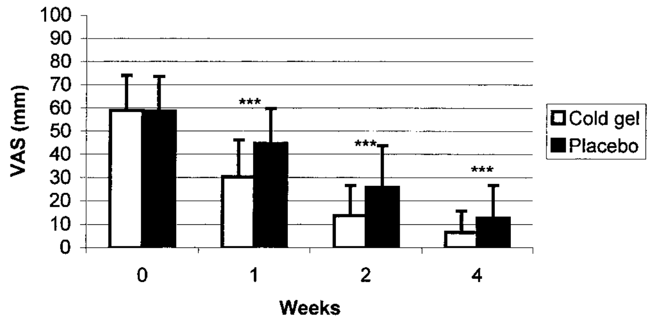

Figure 1. Pain at rest in the active cold gel and placebo gel groups (mean ± SD). ***, statistical significance between the groups ($P < 0.001$).

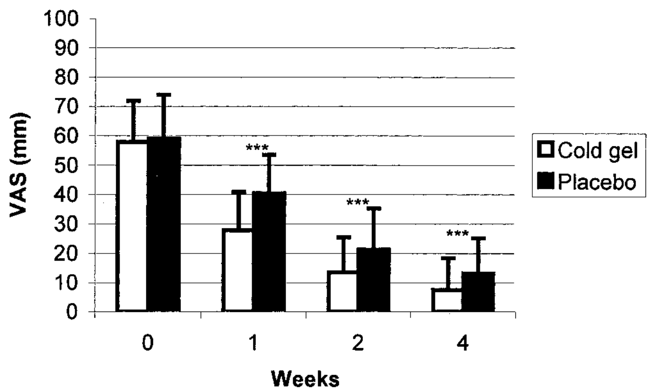

Figure 2. Pain on movement in the active cold gel and placebo gel groups (mean ± SD). ***, statistical significance between the groups ($P < 0.001$).

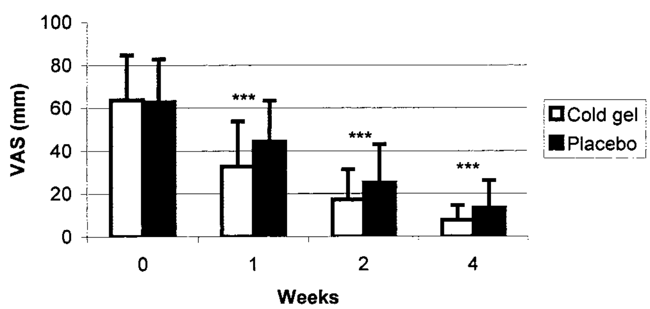

Figure 3. Functional disability measured on a visual analog scale in the active cold gel and placebo gel groups (mean ± SD). ***, statistical significance between the groups ($P < 0.001$).

DISCUSSION

The cellular and molecular mechanisms that enable us to sense cold are not well understood. Menthol elicits a cooling sensation. Recently, a menthol receptor has been characterized and cloned that is also activated by thermal stimuli in the cool-to-cold range. This cold- and menthol-sensitive receptor, CMR1, is a member of the transient receptor potential family of excitatory ion channels, and it has been proposed that it functions as a transducer of cold stimuli in the somatosensory system.[15] If this proposal is found to be correct, it would demonstrate that menthol plays an important role as a cold-mediating factor. In the gel used in our study, the menthol and ethanol were thought to be the active and effective factors.

Cold application is one of the most extensively used treatments for athletic injuries.[3,16,19,20] Cryotherapy for 20 minutes, two to four times a day for the first 2 to 3 days is helpful in promoting an early return to full activity.[13] Recently, a systematic review indicated that ice was an effective modality, but it should be applied in repeated applications of 10 minutes to be most effective, to avoid side effects, and to prevent possible further injury.[14] In our study, we did not measure the decrease of skin temperature or the effects to blood flow in the skin. Our study was concentrated on the global efficacy of cold for pain relief, improvement of function, and recovery from soft tissue injuries. The theoretical mechanisms of cold therapy were based on the positive physiologic effects of cold therapy for tissue recovery after trauma, such as pain relief, decrease of nerve conduction, and decrease of edema by contraction of blood vessels.

The successful use of cold therapy in various modalities has been based on the physiologic knowledge of the effects of cold on injured tissues. The efficacy of cold therapy for soft tissue injuries was evaluated in this present trial in a prospective randomized design, to our knowledge, for the first time. Cold therapy is usually applied with ice packs, ice towels, or crushed ice. In this study, we used a novel cold-forming gel on the skin of the injured area and compared its efficacy to a placebo gel without a cold-producing composition. Our results showed the clear efficacy of active cold gel for reducing pain at rest, pain on movement, and disability, as evaluated on visual analog scales. Also, the patient's and investigator's satisfaction with the therapy was significantly greater for patients in the cold gel group than in the placebo group. The use of regular ice packs requires access to a refrigerator or to special packaging for ice packs. The cold gel can easily be carried by a patient or even tucked conveniently in the pocket of an athlete.

Cold increases the pain threshold, the viscosity, and the plastic deformation of tissues but decreases motor performance.[9,11,12,19] The application of cold has also been found to decrease the inflammatory reaction in experimental conditions.[16,20] However, some of these reactions differ from expectations. Skin, subcutaneous, intramuscular, and joint temperature changes depend on the application method, initial temperature, and application time. Intramuscular temperature continues to drop after the cooling modality has been removed.[16] Cold water immersion may reduce muscle stiffness and the amount of damage after strenuous exercise activity. There appears to be no effect on the perception of tenderness and strength loss, which is characteristic after this form of activity.[8,9] The results of various studies are consistent in that the effects are mediated through neuromuscular and pain processes.

The physiologic basis for cold therapy is assumed to be cold-mediated vasoconstriction leading to decreased edema formation and a reduction in overall tissue morbidity.[4] The acute microvascular effects of cryotherapy are vasoconstriction and decreased perfusion.[2,4,12] However, when cryotherapy was used as a treatment after contusion or sham contusion, there were no long-lasting microvascular effects either in the presence or absence of contusion as assessed by laser-Doppler flowmetry.[4] In general, the results of studies on cold and blood flow vary considerably; however, it appears that blood flow increases with superficial cold application and decreases when cold is applied to large skin surface areas or if the application is long-lasting.[5,11]

Motor performance is affected by temperature, with the critical temperature being around 18°C, below which muscle performance decreases.[5,16,17] Externally applied instant cold packs used in a dog model caused local tissue hypothermia that peaked at 20 minutes, persisted for at least 1 hour, and was significantly augmented by adjunctive compression.[2] Most of these effects produced by cold application are beneficial after soft tissue injury. How deeply the effects of the cold gel used in our study reached could not be evaluated. The novel finding of a menthol receptor[15] would suggest that the cold-mediating effect would be systemic and might be widespread. This speculation will need further investigations of the deep effects of superficial menthol-containing agents, such as the cold gel we used.

Our study did not assess whether the cold gel actually lowered the physical temperature of tissues under treatment. Its mechanism of action may not be the same and it may not produce all the same effects as traditional cryotherapy. Future experiments are necessary to determine whether the gel actually lowers tissue temperature and whether its effects are comparable with those of traditional cryotherapy.

According to some investigations of the use of superficial nonsteroidal antiinflammatory gels, the most sensitive variables in these studies of patients with rheumatoid arthritis and soft tissue injuries were the patient's global assessment, pain, and morning stiffness.[1,10] With certain reservations, due to the slightly different study population, this conclusion applies also to the present study. The most important parameters, evaluation by the patients and pain at rest and movement, showed significant differences favoring the active cold gel therapy.

Frostbite is a recognized danger of the use of cold packs or ice therapy for sports injuries and soft tissue trauma. Cases of nerve palsy resulting from ice application have been reported, although these palsies were temporary; they usually resolved spontaneously without any significant sequelae.[6,7,9] The adverse events in our trial were minimal and did not lead to the discontinuation of the therapy in any patient. In both groups the incidence of side effects was the same, leading to the conclusion that it was the gel composition that caused skin abrasion, not the ethanol or menthol ointments that were responsible for the cold effects. However, only 37 patients were treated with active cold gel in this study. Clinical trials in a much larger number of subjects are necessary to establish the risk of adverse reaction in a broad population.

In conclusion, this prospective randomized controlled trial showed that cold gel caused significantly faster pain relief and significantly faster rehabilitation results after minor soft tissue injuries. All primary and secondary end points favored cold gel therapy. Our results indicated that cold gel was superior to placebo gel and provided an effective and safe treatment for pain and disability for sports-related soft tissue injuries.

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