Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
0(0) 1–15

DOI: 10.1177/0300060519859146
journals.sagepub.com/home/imr
SAGE

Comparison of diclofenac gel, ibuprofen gel, and ibuprofen gel with levomenthol for the topical treatment of pain associated with musculoskeletal injuries

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Abstract

Objective: To determine whether 3% w/w levomenthol added to ibuprofen gel (5% w/w) improves its efficacy compared with ibuprofen gel alone or diclofenac gel (1.16%) for the treatment of soft-tissue injuries.

Methods: A total of 182 patients with acute soft-tissue injuries participated in a randomised, single-blind, single-dose study to assess the efficacy and safety of three topical analgesic gels. Efficacy was assessed as the score change in a numeric rating scale for pain.

Results: The median time to significant pain relief was 20 minutes for the ibuprofen/levomenthol and diclofenac gels but 25 minutes for ibuprofen gel. At 2 hours, significantly more patients treated with ibuprofen/levomenthol gel reported a cooling sensation (45.8%) compared with diclofenac (16.4%) or ibuprofen (14.7%) gels, and both ibuprofen/levomenthol and diclofenac gels provided significantly more effective global pain relief compared with ibuprofen gel. Few adverse events and no serious adverse events related to study medication were recorded.

Conclusions: Although all gels effectively relieved pain, both ibuprofen/levomenthol and diclofenac gels provided superior global pain relief compared with ibuprofen gel, with a shorter

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median time to significant pain relief. Only ibuprofen/levomenthol gel provided cooling for up to 2 hours. None of the gels were associated with serious safety concerns. EudraCT No 2015-005240-33 EU Clinical Trials Register URL: https://www.clinicaltrialsregister.eu/ctr-search/search

Keywords
Analgesic, diclofenac, ibuprofen, levomenthol, menthol, pain relief, topical

Date received: 2 February 2019; accepted: 3 June 2019

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) administered orally or intravenously typically reach relatively high concentrations in the blood to achieve effective tissue concentrations at the site of pain and inflammation. However, these high concentrations can be associated with adverse effects such as dyspepsia and gastrointestinal bleeding. In contrast, topical NSAIDs are applied directly to the painful area, making them less likely to accumulate at physiologically active concentrations elsewhere in the body. The precise formulation of a topical medication may influence the speed of drug absorption. In fact, because formulation chemistry can significantly affect the rate and quantity of drug distribution to subcutaneous injured tissues, the effect of formulation may be as important as the individual NSAID used. Rapid absorption formulations are enhanced by substances that improve skin penetration, and gel formulations are particularly suitable for this purpose.[1] Gels containing the NSAIDs diclofenac, ibuprofen, and ketoprofen are particularly effective in providing pain relief for acute musculoskeletal conditions.[1] Topical menthol, which stimulates thermoreceptors, has also been used to enhance the efficacy of analgesic gels containing NSAIDs.[2] The focus of the present study was to assess the effect of adding levomenthol, a form of topical menthol, to an ibuprofen gel.

Ibuprofen is a non-opioid analgesic and NSAID which reduces pain, stiffness, and inflammation.[1] It is used to treat the symptoms of osteoarthritis, rheumatoid arthritis, and gout. Ibuprofen is a cyclooxygenase (COX) inhibitor and its analgesic and anti-inflammatory properties are particularly effective in treating soft-tissue injuries when topically applied. A recent review of topical NSAIDs noted that ibuprofen gel demonstrated high clinical efficacy in the treatment of acute musculoskeletal pain in adults, with a number-needed-to-treat (NNT) value of 3.9 (95% confidence interval [CI], 2.7–6.7) from two studies with outcomes of marked improvement or complete remission.[1] Ibuprofen has fewer side-effects and a lower risk of gastrointestinal bleeding and ulceration than many other NSAIDs.[3] A major advantage of applying NSAIDs directly to the affected area in gel form is that targeted pain relief can be achieved without systemic side-effects.[1,4]

Diclofenac, another NSAID, exerts an anti-inflammatory effect and can be administered regularly over an extended period to relieve pain and stiffness associated with rheumatoid arthritis and advanced osteoarthritis.[3] Diclofenac is effective in treating various types of acute and chronic pain and inflammatory conditions. As with all NSAIDs, diclofenac inhibits prostaglandin synthesis by inhibiting COX-1 and COX-2. However, recent research has demonstrated that the pharmacological activity of diclofenac extends beyond COX inhibition.

Diclofenac may inhibit the thromboxane-prostanoid receptor, affect arachidonic acid release and uptake, inhibit lipoxygenase enzymes, and activate the nitric oxide-cGMP antinociceptive pathway.[5] The Emulgel® formulation of diclofenac has a very high clinical efficacy in treating acute musculoskeletal pain in adults, with an NNT value of only 1.8 (95% CI, 1.5–2.1) as demonstrated in two studies using at least 50% pain intensity reduction as the outcome measurement.[1]

Menthol is an alcohol from mint oils used as an inhalation and topical antipruritic.[3] It can exist in two enantiomeric forms (+/–), occurring as levomenthol (–) or racemic menthol (±).[6] Levomenthol is the most abundant optical isomer and is the form used in menthol gel products. Menthol reportedly acts as a 'cooling-mimetic' agent, producing the sensation of cooling without reducing skin temperature.[7,8] Following topical application, menthol stimulates thermoreceptors to generate cold or warm sensations, and has an anaesthetic effect.[2,9,10] Menthol can also enhance the skin penetration of topical analgesics and may increase their effectiveness in relieving pain.[2] In addition, many topical analgesic treatments are formulated in an aqueous/alcoholic gel, and this preparation has a soothing and rapid cooling effect when applied to the skin.[11]

The aim of this study was to investigate whether adding levomenthol to an ibuprofen gel reduced the time taken for a significant analgesic effect to occur in patients with soft-tissue injuries. We applied different gels and collected self-reported pain relief data over a 2-hour assessment period. We also measured other parameters (including cold/warm sensations) that might be linked to analgesia to determine whether the addition of levomenthol enhanced the performance of ibuprofen gel. Comparisons were also made with a gel containing diclofenac, generally considered the most effective topical NSAID.[1,12]

Patients and methods

Study design

This was a single-centre, randomised, single-blind, parallel-group, single-dose study of the efficacy of ibuprofen gel (5% w/w) containing 3% w/w levomenthol (ibuprofen/levomenthol gel) for the treatment of strains, sprains, and sports injuries. The efficacy of this gel was compared with that of ibuprofen gel (5% w/w) without levomenthol and with a gel containing diclofenac (1.16%).

Study measures

The primary objective of the study was to determine the time to significant pain relief for patients with soft-tissue injuries who were treated using ibuprofen gel, ibuprofen/levomenthol gel, or diclofenac gel. Significant pain relief, the primary endpoint for our study, was defined as a reduction of 2 points on an 11-point numeric rating scale (NRS) for pain.[13,14] Study participants also provided information at specific time points regarding any cooling/warming sensations they experienced, and evaluated the gels for analgesic efficacy (11-point NRS) and level of global pain relief (7-point NRS) at 2 hours after gel application.

Sample size calculation

The sample size calculation was performed using Minitab statistical software (ver. 17; Minitab Ltd., State College, PA, USA) based on a three-group, one-way analysis of variance. Assuming a standard deviation for time to pain relief of 8 minutes, a sample size of 51 was required for each group to detect a between-group difference of 5 minutes at 80% power and 5% significance level. To allow for non-parametric

testing, we applied a rule of thumb that recommended increasing the parametric sample size estimate by 15%.[15] The sample size for this study was therefore 60 patients per group.

Recruitment

All study participants had experienced an acute soft-tissue injury and were recruited via referral from local pharmacies and healthcare professionals or by responding to study advertisement. Potential participants were screened to determine whether they were suitable for the study using specific inclusion and exclusion criteria. Suitable participants attended a clinic appointment and were shown how to complete the assessments on an electronic device. Patients were unaware that a pain assessment of 6 or greater on an 11-point NRS for pain was required to enter the study. Patients who met this requirement and all other inclusion/exclusion criteria were randomised 1:1:1 to one of the three treatments. The study was approved by the East of Scotland Research Ethics Service (EoSRES) REC2 (16\ES\0009), and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to undergoing any study procedures.

Inclusion and exclusion criteria

Male and female patients between the ages of 16 and 75 years (inclusive) were eligible for participation. Patients with an acute soft-tissue injury who reported being in at least moderate pain at baseline ($\geq$6 on an 11-point NRS for pain) were enrolled in the study, unless any of the following exclusion criteria were applicable: inflamed or broken skin in the area to be treated; allergy to aspirin, NSAIDs, or any of the gels' ingredients; chronic injury, active peptic ulcer, or significant renal disease; pregnancy or lactation; use of an analgesic treatment within the preceding 8 hours or a slow-release/long-lasting analgesic treatment within the preceding 24 hours; history of severe hepatic impairment or alcohol abuse; participation in a clinical trial within the preceding 30 days.

Study procedures

Eligible patients who met the inclusion and exclusion criteria were randomised to receive one of the three gel treatments using a computer-produced randomisation schedule where each eligible patient was allocated the next available unique patient number. Following baseline assessments and instructions on how to record pain levels using a standard tablet, patients had gel applied by a healthcare professional in accordance with product instructions. The patient was then supervised by another member of the research team during the 2-hour assessment period. Therefore, both the patients and the investigators supervising the assessments were blinded to the randomisation schedule. The assessment rooms were "mentholised" to mask the distinctive odour of levomenthol. Drug supplies were prepared and labelled according to Good Clinical Practice. Patient data were collected using a customised tablet program, stored on an internal database within the application, and subsequently uploaded to a local database server. Patients were prompted electronically to ensure accurate completion of each assessment. The member of staff supervising the assessments also prompted patients to record their pain levels at each of the time points.

Data collection

Patients completed 11-point NRS (pain) and 11-point warming/cooling scale (WCS) evaluations at 17 time points (1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40,

50, 60, 75, 90, 105, and 120 minutes). In addition, a global assessment of pain relief was made on a 7-point scale ('no relief' to 'complete relief') at the end of the 2-hour period.

Adverse events

Patients were asked whether they had any untoward symptoms other than their injury prior to gel application and at the end of the 2-hour assessment period. In addition, patients were followed up by telephone 1 to 3 days after the assessment and asked to provide details of any adverse or serious adverse events they had experienced in the intervening period. Each event was recorded and its likely relationship to study medication was determined by a medically qualified trial investigator.

Statistical analysis

Primary outcome. The primary outcome for this study was the time to significant pain relief, defined as a two-point decrease in pain score from baseline and analysed at 30 and 120 minutes after gel application using survival analysis (log-rank test) performed at a 5% significance level. The survival analysis method was used because some study participants may not experience significant pain relief at the end of the 2-hour assessment period.

Secondary outcomes. Analgesic efficacy at 2 hours, defined as the median difference in pain score between baseline and 2 hours, was analysed using a Kruskal–Wallis test performed at a 5% significance level. To assess whether there was an association between treatment group and experience of cooling at 2 hours following application, herein referred to as cooling effect, a Pearson chi-squared test was performed at the 5% significance level. Differences in global pain relief at 2 hours and the level of pain relief experienced at this time point were compared between the different treatments using a Kruskal–Wallis test performed at a 5% significance level. All primary and secondary analyses were performed using Minitab statistical software (ver. 17; Minitab Ltd.).

Results

Demographic and injury data

Age and gender data for the study population are shown in Table 1. Of the 182 participants recruited to the study, 109 (59.9%) were male and 73 (40.1%) were female. The mean age of study participants was 36.18 years (range: 17–67 years) and was similar for males (36.65 years) and females (35.47 years).

Table 2 summarises the injuries reported by the study participants. Of the 182 individuals who took part in the study, 137 (75.27%) reported having an injury duration of more than 1 week, 27 (14.84%) reported a duration of 4 to 7 days, and 18 (9.89%) reported a duration of 1 to 3 days. The most common injury site was a lower limb (79 participants). Sprains and strains were the most common type of injury, reported by 129 study participants (70.88%). Muscular aches were reported by 42 study participants (23.08%), whereas 11 individuals (6.04%) reported bruising or soft tissue injuries. A total of 104 (57.14%) study participants were affected by sporting injuries. Injury types and durations were

Table 1. Age distribution (years) of the 182 study participants.

	Mean age (years)	Standard deviation	Range
Study ($n = 182$)	36.18	12.09	17–67
Men ($n = 109$, 59.9%)	36.65	13.17	17–67
Women ($n = 73$, 40.1%)	35.47	10.32	18–57

Table 2. Injuries reported by study participants.

	Number (N = 182)	% of total
Duration of injury (days)		
<1	0	0.00
1–3	18	9.89
4–7	27	14.84
>7	137	75.27
Site of injury		
Neck	14	7.69
Shoulder	29	15.94
Upper limb	15	8.24
Back	45	24.73
Torso	0	0.00
Lower limb	79	43.41
Type of injury		
Sprain/strain	129	70.88
Muscular ache	42	23.08
Bruising/soft tissue	11	6.04
Sporting injury		
Yes	104	57.14
No	78	42.86

similar among the three randomised gel treatment groups. There were fewer neck injuries in the diclofenac (1) than in the ibuprofen (6) or ibuprofen/levomenthol (7) gel treatment groups. However, there were only 14 neck injuries in total, so this was unlikely to have had a significant effect on the results.

Study participation

Of the 182 study participants, 181 completed the 2-hour assessment. One participant was unable to provide responses on the tablet because of an error in the data collection system; this patient's data were not collected manually or analysed. Of the 181 participants who completed the assessment, 59 had been randomised into the ibuprofen/levomenthol gel treatment group and 61 each had been randomised into the diclofenac and the ibuprofen gel groups. The patient who failed to complete the assessment period had been randomised to the ibuprofen/levomenthol gel group. In total, some time-point data were missing from 13 patients, but this constituted only 0.6% of all pain data. Of the 182 participants, 180 completed the telephone follow-up. Two participants (both from the ibuprofen treatment group) failed to complete the telephone follow-up.

Time to pain relief

Application of ibuprofen/levomenthol gel or diclofenac gel resulted in a shorter median time to significant pain relief (20 minutes) compared with application of the ibuprofen gel (25 minutes). Additional survival analyses were performed to allow the inclusion of data from patients who failed to reach the primary endpoint defined as significant pain relief (a two-point drop in pain score from baseline). These survival analyses, shown in Figure 1, did not result in statistically significant differences among the three treatment groups at 30 minutes or 120 minutes. However, at the 30-minute time point, 71.2% of patients in the ibuprofen/levomenthol gel group reported a 2-point reduction in pain score compared with only 55.7% of patients in the ibuprofen gel group (Figure 2). We calculated that a study population of approximately 160 patients per group might have shown a statistically significant difference between the ibuprofen/levomenthol gel and ibuprofen gel treatments at 30 minutes. Although a statistically significant difference was not demonstrated, Figure 2 shows that throughout the 2-hour assessment period, more patients who used ibuprofen/levomenthol gel or diclofenac gel tended to report significant pain relief compared with patients who used ibuprofen gel.

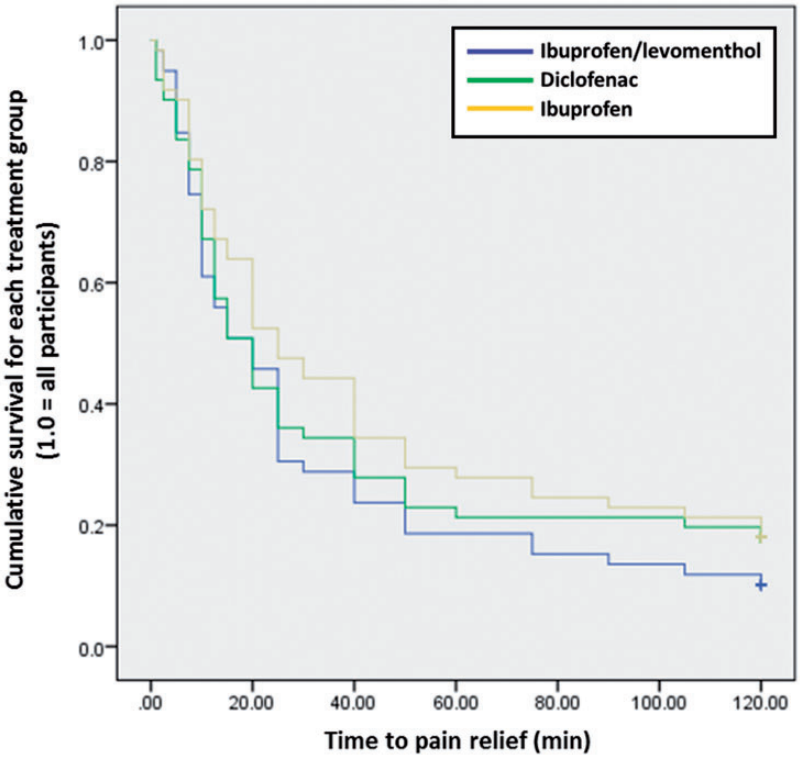

Figure 1. Survival analysis showing the proportion of patients yet to report significant pain relief (2-point reduction in pain score from baseline) at successive time points.

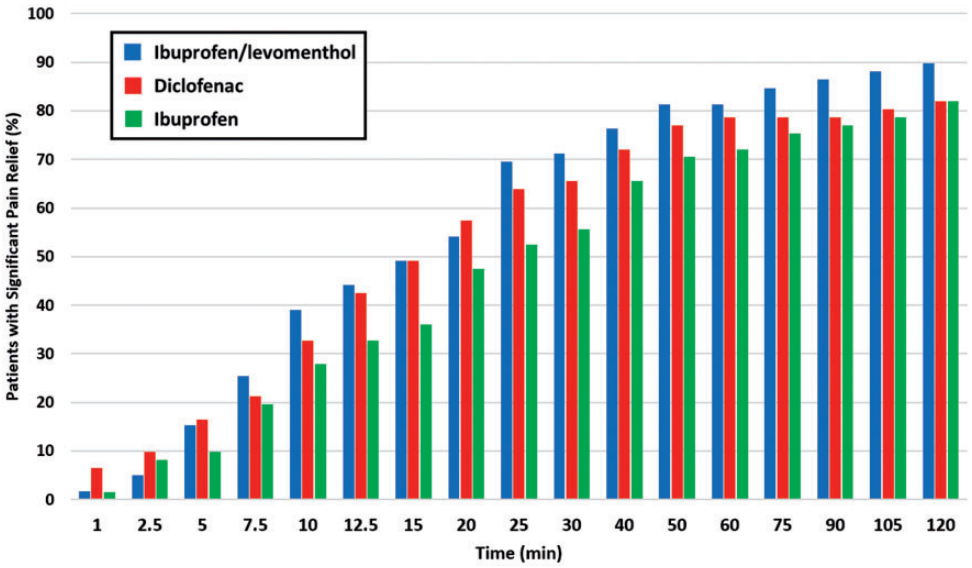

Figure 2. Proportion of patients achieving significant pain relief at each time point.

Analgesic efficacy at 2 hours

We also determined analgesic efficacy 2 hours after gel application (Table 3). For each treatment group, we calculated the median change in pain score (11-point NRS for pain) between baseline and the 2-hour time point. The median score change was –3 for the ibuprofen/levomenthol and diclofenac gels and –2 for the ibuprofen gel. Tests for differences among the three groups failed to reach the level of statistical significance ($p = 0.070$). The mean changes shown in Table 3 are descriptive only.

Cooling effect

At 2 hours after gel application, significantly more patients in the ibuprofen/levomenthol gel treatment group reported cooling (45.8%) compared with the diclofenac (16.4%) and ibuprofen (14.7%) groups ($p < 0.001$). The differences in cooling data collected over 17 time points during the 2-hour assessment period are shown in Figure 3. This result indicates that only the ibuprofen/levomenthol gel provided prolonged cooling, attributable to the presence of levomenthol. Note that the study design

Table 3. Median changes in pain scores between baseline and 2 h.

	Total patients (*n*)	Mean baseline score	Mean score at 2 h	Median change	IQR	Mean change
Ibuprofen/levomenthol	59	7.2	4.0	−3.0	(−5.0, −2.0)	−3.373
Diclofenac	61	7.2	4.4	−3.0	(−4.0, −1.0)	−2.705
Ibuprofen	61	7.2	4.5	−2.0	(−4.0, −1.0)	−2.705

IQR: inter-quartile range.

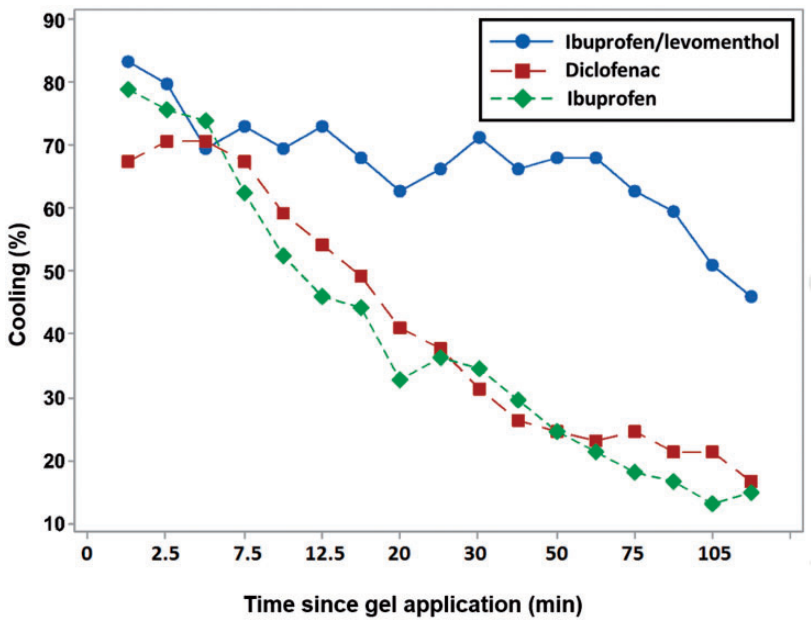

Figure 3. Association of ibuprofen/levomenthol gel with prolonged cooling.

prevented patients reporting cooling at a particular time point if they had already reported warming at the same time point.

Global pain relief at 2 hours

All 181 participants who completed the 2-hour assessment period were asked to rate the level of global pain relief they had experienced. NNT values were also calculated based on the number of patients who experienced moderate pain relief or better. The results are shown in Table 4.

The global pain relief data were coded to a 7-point scale and a statistically significant difference was found in the median global pain values among the three groups (Kruskal–Wallis test, $p = 0.006$). There was no significant difference in median global pain relief between the ibuprofen/levomenthol gel and diclofenac gel groups, but treatment with either of these gels resulted in a superior outcome compared with treatment with ibuprofen gel that was equivalent to 1 point on the scale. This result, as shown in Figure 4, indicates that the median result of treatment with ibuprofen gel is 'mild relief,' whereas the median result of treatment with ibuprofen/levomenthol gel or diclofenac gel is 'moderate relief.' This statistically significant 1-point difference was observed on the 7-point scale and not on the 11-point NRS used in the other analyses.

Adverse events

No adverse events were recorded during the in-clinic assessment period. Subsequent adverse events recorded at follow-up are listed in Table 5. In total, seven adverse events were recorded, five of which were categorised as unrelated to study medication. One adverse event, where the patient reported a warming sensation on the neck, was judged 'unlikely' to be related to the study. The remaining adverse event, where the patient reported 'red itchy skin where gel applied', was judged as 'definitely' related to the study medication. Both of these patients were from the diclofenac treatment group. A single serious adverse event was recorded (Table 6), in which the patient required surgery to pin a fractured fibula. This serious adverse event was evaluated as unrelated to study medication.

Discussion

The purpose of this study was to assess the effect of adding levomenthol to ibuprofen gel. Diclofenac gel was included as a relevant comparator. The study assessed the efficacy and safety of these three topical analgesic

Table 4. Number of patients in each treatment group reporting each level of global pain relief at 2 h.

	Ibuprofen/levomenthol gel ($n = 59$)	Diclofenac gel ($n = 61$)	Ibuprofen gel ($n = 61$)
No relief	1 (1.7%)	4 (6.6%)	5 (8.2%)
Slight relief	10 (16.9%)	10 (16.4%)	14 (23.0%)
Mild relief	15 (25.4%)	13 (21.3%)	14 (23.0%)
Moderate relief	6 (10.2%)	21 (34.4%)	14 (23.0%)
Considerable relief	18 (30.5%)	10 (16.4%)	9 (14.8%)
Almost complete relief	7 (11.9%)	2 (3.3%)	4 (6.6%)
Complete relief	2 (3.4%)	1 (1.6%)	1 (1.6%)
NNT ($\geq$moderate relief)	1.79 (95% CI, 1.45–2.36)	1.79 (95% CI, 1.46–2.36)	2.18 (95% CI, 1.69–3.02)

NNT: number needed to treat; CI: confidence interval.

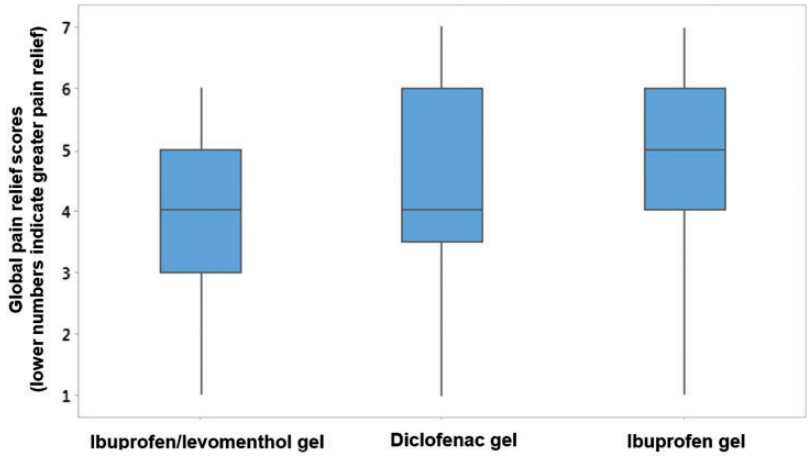

Figure 4. Between-group comparison of global pain relief at 2 hours.

Table 5. Adverse events.

Treatment	Age	Sex	No. of events	Event	Severity	Related to study
Diclofenac	59	M	1	Warming sensation on neck	Mild	Unlikely
Diclofenac	31	M	1	Red itchy skin where gel applied	Mild	Definitely
Ibuprofen/ levomenthol gel	42	F	1	Swelling to feet and ankles	Mild	None
Ibuprofen	43	M	2	1: Feeling high temperature	Mild	None
				2: Night sweats	Mild	None
Diclofenac	18	M	2	1: Pressure at base of back	Mild	None
				2: Pressure on forehead	Mild	None

F, female; M, male.

Table 6. Serious adverse event.

Treatment	Age	Sex	No. of events	Event	Severity	Related to study
Diclofenac	48	M	1	Operation to pin fractured fibula	Moderate	None

M, male.

gels for the treatment of soft-tissue injuries. We found that all three gels provided effective pain relief. No serious adverse events related to study medication were reported, and only one adverse event of mild severity was considered related to study medication (diclofenac). Although the time to pain relief results did not demonstrate statistically significant differences, the ibuprofen/levomenthol gel and diclofenac gel had shorter median times to significant pain relief than the ibuprofen gel. Of the three gels, only the

ibuprofen/levomenthol gel provided prolonged cooling for up to 2 hours after gel application. In addition, there was a statistically significant difference in median global pain relief among the three treatment groups 2 hours after gel application; no difference was observed between the ibuprofen/levomenthol gel and the diclofenac gel, but treatment with either of these gels resulted in a superior outcome compared with ibuprofen gel treatment. This finding indicates that the addition of levomenthol to ibuprofen gel not only produces a potentially beneficial cooling effect but might also enhance its analgesic efficacy.

NRSs were selected as appropriate for the quantification of pain relief in our study based on a systematic literature review that included 54 studies assessing pain intensity in adults with postoperative pain, cancer, and other conditions. The authors considered compliance rates, responsiveness, ease of use, and applicability of different pain scales and found that an NRS was applicable for unidimensional assessment of pain intensity in most settings.[16]

The primary endpoint for our study was the time to onset of significant pain relief, which was defined as a reduction of two points on an 11-point NRS for pain. However, not all patients achieved this level of pain relief by the end of the 2-hour assessment period. The UK Medicines and Healthcare products Regulatory Agency has stated that "It is unlikely that a time to onset of relief of more than 30 minutes would be considered to be 'fast' for a product for relief of an acute condition."[17] Consequently, the median time to significant pain relief was reported for each gel. For both the ibuprofen/levomenthol and the diclofenac gels, this was shorter (20.0 minutes) than that for the ibuprofen gel (25.0 minutes), indicating that the ibuprofen/levomenthol gel and the diclofenac gel were faster acting. However, the median time to significant pain relief was less than 30 minutes for all three gels.

Regardless of aetiology, pain is a subjective experience communicated only through words and behaviours, and the measurement of pain relief is extremely difficult.[18] We defined a reduction of two points on an 11-point NRS for pain as 'significant pain relief' and considered this two-point change to be sufficiently large to be accepted as clinically significant, that is, to have a meaningful effect on a patient's daily life. Interestingly, a study by Kelly (1998) on visual analogue scales (VAS) for pain found that a 9-mm difference on a 100-mm VAS scale was clinically significant. This difference would correspond to a one-point change on the 11-point scale used in our study,[19] and would have meant that more patients would have reached the study endpoint. Following the study, we performed a number of additional analyses to assess efficacy differences between ibuprofen/levomenthol gel and ibuprofen gel. If significant pain relief had been defined as a one-point reduction in pain score then at 30 minutes, 95% of patients who received ibuprofen/levomenthol gel reported significant pain relief compared with 82% of patients in the ibuprofen gel group, and this difference would have been statistically significant ($p = 0.023$).

Other studies have also found that relatively small changes in pain scores can be clinically significant. Kendrick and Strout (2005) found that a change of 1.39 (± 1.05) was clinically significant when measuring pain in a study of 354 emergency department subjects who were asked to rate their pain on an 11-point NRS every 20 minutes.[14] In addition, Myles et al. (2017)[20] studied an unselected cohort of patients recovering from surgery and found that analgesic interventions that produce a change of 10 mm on a 100 mm VAS signify a clinically important change in a patient's pain status.

However, clinically significant changes in pain scores may vary considerably among

studies. Olsen et al. (2017)[21] reviewed 37 studies on acute pain and found that among 29 suitable studies that used a mean change approach, absolute minimal clinically important differences in pain scores ranged from 8 to 40 mm with a median of 17 mm on a standardised 100-mm scale. Clearly, a given treatment could have a statistically significant effect that is not clinically significant.

Clinical efficacy may also be measured by calculating NNT values. In two studies that used outcomes of marked improvement or complete remission, ibuprofen gel had an NNT value of 3.9 for treating acute musculoskeletal pain in adults.[1] In a similar patient population, the Emulgel® formulation of diclofenac had an NNT value of 1.8 in two studies that used at least 50% pain intensity reduction as the outcome.[1] Using the outcome of moderate pain relief or better on our 7-point global pain relief scale, we found that the ibuprofen/levomenthol and diclofenac gels both had the same NNT value (1.79), whereas the NNT value for ibuprofen gel was slightly higher (2.18; Table 4). Interestingly, analysis of our 11-point NRS pain data using the outcome of at least 50% pain intensity reduction also produced a slightly higher value for ibuprofen gel (NNT = 2.10) than for diclofenac (NNT = 1.65) and ibuprofen/levomenthol (NNT = 1.44) gels.

In addition to investigating the time to pain relief as a 2-point drop in pain score from baseline, we evaluated the level of global pain relief reported by patients at the end of the 2-hour assessment period using a 7-point scale. We found no difference in median global pain relief between ibuprofen/levomenthol gel and diclofenac gel, but treatment with either of these gels resulted in a 1-point superior outcome compared with treatment with ibuprofen gel. Because this statistically significant difference was observed on a 7-point scale and not the 11-point NRS used in the other analyses, it is more likely to be clinically important.

A strength of our study was that only participants with high baseline pain levels were included, thus ensuring that effective treatment would cause a larger change in pain intensity than less effective treatment.[13] In addition, conducting the 2-hour assessment at the clinic meant that patients could be monitored throughout and increased the likelihood that pain scores were entered accurately at the correct time points, compared with asking patients to complete a home-based treatment diary.

This study had some limitations, however. Although we used a power calculation to determine the number of patients to recruit, this calculation reflected our definition of significant pain relief for the primary outcome (a reduction of two points on an 11-point NRS). As noted in the results section, a larger patient population might have allowed statistically significant differences in pain relief to be identified when levomenthol is added to an ibuprofen gel. In addition, as discussed above, clinically significant changes in pain scores may vary considerably among studies. Consequently, we cannot be certain that the changes reported in our study are clinically meaningful.

A recent study demonstrated that both a gel containing levomenthol and a placebo gel with no levomenthol could decrease skin temperature and intramuscular temperature in the quadriceps of the anterior thigh. The gel containing levomenthol increased cutaneous blood flow, whereas the placebo gel did not. The gel containing levomenthol was also subjectively reported to be cooler.[22] In the present study, the effect of adding levomenthol to a pain relief gel could be isolated. The only substantive difference in composition between the ibuprofen/levomenthol gel and ibuprofen gel used in our study was the presence of levomenthol in the ibuprofen/levomenthol

gel. The 3% w/w levomenthol in the ibuprofen/levomenthol gel was replaced by 3% w/w purified water in the ibuprofen gel. Therefore, differences in efficacy between these two gels appear to be associated with levomenthol and cannot be attributed to gel alcohol content. At the end of the 2-hour assessment period, significantly more patients in the ibuprofen/levomenthol gel treatment group reported cooling (45.8%) compared with the diclofenac (16.4%) and ibuprofen (14.7%) gel groups. At this 2-hour time point, there was a significant association between reported cooling and treatment group ($p < 0.001$).

With respect to the evaluation of temperature perception, it is important to note that the study design prevented patients from reporting warming and cooling sensations at the same time point. The main reason for this was that the earlier time points in the study were at shorter intervals, and it was critical that patients had sufficient time to answer all required questions. Patients were first asked whether they experienced warming, and those who answered "yes" were not asked whether they experienced cooling at that particular time point. That is, we assumed that patients who experienced warming would not have experienced cooling simultaneously.

We also performed supplementary statistical analyses to evaluate different but related analgesic parameters. However, the relatively small size of the study population made it difficult to demonstrate differences in analgesic performance among the gels at the 5% CI.

Our study compares favourably with similar recent investigations that have used NRSs to assess pain changes. Bussin et al. (2017) performed a pilot study in 19 adults with chronic Achilles tendinopathy to evaluate successive treatment with either 10% diclofenac or placebo gel over a 3-day period. The primary outcome measure was pain level on an 11-point NRS during hopping, which was reduced on average from 4.8/10 to 3.1/10 by diclofenac.[23] The use of chronic conditions to assess the effectiveness of topical pain relief gels facilitates the use of a more rigorous crossover study design, although it can be more difficult to demonstrate a clinically significant improvement in pain scores. Lai et al. (2017)[2] used four-times-daily treatment with 1% diclofenac/3% menthol gel in adolescents and adults with acute ankle sprain. They measured the area under the curve of pain intensity on movement from 24 to 72 hours post-application using an 11-point NRS for pain and found no significant improvement compared with placebo, 1% diclofenac, or 3% menthol gel. However, other studies have demonstrated the efficacy of diclofenac gel in treating acute ankle sprains.[24,25]

Our study demonstrated that all three gels had a median time to significant pain relief of less than 30 minutes. Additionally, the ibuprofen/levomenthol gel was able to provide prolonged cooling for up to 2 hours after gel application. Clearly, the clinical implication of faster pain relief is that patients spend less time in pain, while the rapid onset of pain relief is very important to patients.[26] Cold treatment, typically ice, is frequently used as an immediate treatment for acute musculoskeletal injuries. The application of ice has been linked to reductions in tissue metabolism, haematoma formation, inflammation, and tissue necrosis. In addition, treatment with ice is associated with analgesia and may accelerate the regeneration of muscle tissues.[27–31]

Further studies are required to determine the precise clinical benefits of cooling in the treatment of acute musculoskeletal injuries. In addition, any overlap in the mechanistic pathways by which ice and menthol produce cold sensations must be investigated in detail to understand whether benefits conferred by cold temperature can also be

gained by using analgesic gels containing menthol.

Conclusions

The addition of levomenthol to ibuprofen gel was associated with improved analgesic performance when compared with a gel containing only ibuprofen. While all three gels were associated with effective pain relief, our results indicate that ibuprofen/levomenthol gel and diclofenac gel had a shorter median time to significant pain relief compared with ibuprofen gel, although statistically significant differences were not demonstrated. Based on median global pain relief 2 hours after application, ibuprofen gel containing levomenthol produced pain relief that was superior to that of standard ibuprofen gel and similar to that of diclofenac gel. Only ibuprofen/levomenthol gel provided prolonged cooling for up to 2 hours after gel application. No serious adverse events related to study medication were recorded in any patients, and no adverse events related to study medication were recorded in any patients treated with either ibuprofen/levomenthol gel or ibuprofen gel.

Acknowledgements

The authors wish to thank Bobby Brown and Clare Douglas who provided medical writing assistance.

Declaration of conflicting interest

CB is an employee of The Mentholatum Company Ltd.

Funding

This work was supported by The Mentholatum Company Ltd.

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