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Efficacy and safety of topical diclofenac/menthol gel for ankle sprain: A randomized, double-blind, placebo- and active-controlled trial

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Abstract

Purpose: This study was performed to evaluate topical 1% diclofenac/3% menthol gel in treating ankle sprain.

Design: In this randomized, double-blind, placebo-controlled trial, adolescents and adults with acute ankle sprain (N = 385) applied 4 g of gel containing 1% diclofenac/3% menthol (n = 117), 1% diclofenac (n = 112), 3% menthol (n = 77), or placebo (n = 75) four times daily. The primary outcome was the area under the curve of pain intensity (PI) on movement [0 (no pain) to 10 (extreme pain)] from 24 to 72 hours post-application ($AUC_{1-3\ days}$). Secondary outcomes included pain relief (PR); PI; time to onset of PR, meaningful PR, cooling, and complete recovery; PI difference; sum of PI difference; total PR; reduction in ankle swelling; and the patient's global assessment of response to treatment.

Results: There were no statistically significant differences in AUC_{1-3} between 1% diclofenac/3% menthol and placebo, diclofenac, or menthol gels and no meaningful advantages of 1% diclofenac/3% menthol for any secondary outcome. There was a higher incidence of skin and application-site events with 1% diclofenac/3% menthol than with placebo or 1% diclofenac.

Conclusion: No significant improvement was observed with topical 1% diclofenac/3% menthol gel compared with placebo, 1% diclofenac, or 3% menthol gel in treating pain from ankle sprain.

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Introduction

Ankle sprain is a common musculoskeletal injury, particularly among physically active individuals.[1–3] The most common form of ankle sprain involves plantar flexion and inversion, which results in damage to the lateral stabilizing ankle ligaments, including the anterior talofibular ligament, calcaneofibular ligament, and posterior talofibular ligament.[3,4] Depending on the severity of the sprain, these ligaments may be stretched, partially torn, or completely ruptured.[4] In severe sprains, additional structures, including tendons, nerves, muscles, and other ligaments, may also be injured.[3] These injuries can lead to pain, swelling, loss of function, and reduced range of motion.[3]

Standard care for ankle sprain includes rest, ice, compression, and elevation (known as the RICE protocol); early weight bearing with support (depending on severity); manual therapy; and functional rehabilitation.[3,4] Oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as supportive therapy to reduce pain, swelling, and disability and improve function in patients with ankle sprain.[5,6]

Topical NSAIDs work locally to provide short-term pain relief (PR) while potentially reducing systemic side effects (e.g., gastrointestinal effects) that may occur with orally administered NSAIDs.[7,8] Topical diclofenac gel is used to treat pain associated with osteoarthritis and other musculoskeletal disorders, including ligament, tendon, muscle, and joint conditions characterized by pain and inflammation.[7]

Topical menthol stimulates thermoreceptors, resulting in sensations of either cooling or warmth, and has an anesthetic effect.[9,10] Menthol, which is lipophilic and causes local vasodilation, has been shown to enhance skin penetration when added to topical analgesics such as tetracaine or diclofenac; menthol may also enhance the analgesic effects of these agents, as previously demonstrated with tetracaine.[9,11–13]

Whether combining a topical NSAID with topical menthol will improve PR remains unknown. This study was conducted to evaluate the efficacy and safety of a combination 1% diclofenac/3% menthol gel in treating ankle sprain in adolescents and adults.

Materials and methods

Study design and procedures

This randomized, double-blind, placebo-controlled trial involved patients with ankle sprain at 16 centers in Germany from 13 November 2013 to 22 March 2015 (ClinicalTrials.gov Identifier: NCT02100670). Eligible patients were randomly assigned to receive 4 g of topical 1% diclofenac/3% menthol gel, 1% diclofenac/0.09% menthol gel, 3% menthol gel, or placebo gel with 0.09% menthol four times daily at 4- to 6-hour intervals either until complete resolution of pain and swelling or for 10 days, whichever occurred first. The diclofenac in the 1% diclofenac/0.09% menthol gel represented the active control; the amount of menthol was subtherapeutic and added for its fragrance to maintain investigator and patient blinding to the treatment assignments. The patients received training in correct application of the gel and a marked applicator strip to facilitate correct dosing, and application of the first dose was supervised. The marked applicator strip contained two circles with an X marked in the center of each; the patients were instructed

to squeeze the tube to dispense the gel into the center of each circle until the gel filled the circle completely, which provided a dose of approximately 4 g.

Randomization numbers were assigned to eligible patients in ascending numerical order, with both patients and key staff blinded to the treatment allocation. The randomization schedule was provided by the Biostatistics Department of GlaxoSmithKline Consumer Healthcare using their internal randomization process, which ensures concealment of the treatment code identifier. A block randomization method was used to randomize the patients into the four treatment groups in a 3:3:2:2 ratio. The randomization was stratified by site and age group (Stratum 1: 16- to 17-year-old patients; Stratum 2: 18- to 65-year-old patients).

The patients remained at the clinic site for 1 hour after the first dose. They completed and recorded subsequent treatment applications and assessments using a paper diary card at home. The patients then returned to the clinic on days 3 and 7 for follow-up and on day 10 for the final evaluation. They recorded pain intensity (PI) at baseline and then recorded PI and PR at 10 and 30 minutes; at 1, 4, 6, 12, 18, and 24 hours after the first dose; and then twice daily on days 2 through 10. PI was recorded at rest and on movement (walking 5 steps on a flat surface) using an 11-point numerical rating scale (NRS) with scores of 0 (no pain) to 10 (extreme pain). The PR score (PRS) was recorded using a 5-point categorical scale of 0 = no PR, 1 = a little or perceptible PR, 2 = meaningful PR, 3 = a lot of PR, and 4 = complete PR. The patients also rated (yes/no) whether they had a cooling sensation at 10 and 30 minutes after each dose application and at 1, 4, and 6 hours.

The investigator (or designee) assessed ankle swelling by measuring the perimeter using the "figure-of-eight" method[14] at baseline and on days 3, 7, and 10. At the end of treatment, the investigator assessed patients' ankle function, and the patients completed a questionnaire regarding their global assessment of the response to treatment on a 5-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent). The patients were contacted via telephone 6 (±1) days post-treatment to collect additional safety data.

Paracetamol was dispensed for use as a rescue medication (1000 mg every 6 hours as needed based on the patient's opinion, not to exceed 4 g/day; patients were encouraged to wait at least 2 hours after applying the topical study medication before using the rescue medication). Use of other analgesics was prohibited during the study, with the exception of aspirin (81 mg/day or 325 mg/day) for cardiac prophylaxis.

This study was approved by independent central and local institutional review boards and conducted in accordance with the requirements specified in the Declaration of Helsinki. All patients provided written informed consent.

Study population

The patients were aged 16 to 65 years and had a unilateral grade I or II acute sprain of the lateral or medial ankle that had occurred within 24 hours of presentation to one of the clinic sites based on the patient's self-report. Enrollment was limited to those whose injury occurred within 24 hours of presentation because PI from ankle sprain largely decreases after 1 or 2 days. Thus, the greatest potential for a treatment benefit and an opportunity to observe a treatment effect would be anticipated within the first 24 hours after injury. The patients were recruited by placing advertisements in pharmacies close to the study center and in sports facilities/clubs, as well as by providing information about the study directly to trainers to encourage referral. In addition, some of the investigators were present during

evening or weekend sports events (e.g., soccer), where they directly recruited players who experienced ankle sprain.

The inclusion criteria were an ankle PI score of $\geq$5 on an 11-point NRS, at rest or during movement, and perimalleolar edema (submalleolar perimeter difference of $\geq$20 mm between the injured and uninjured ankles as assessed using the ''figure-of-eight'' method). All patients were required to be in good physical and mental health and able and willing to comply with the study procedures and restrictions, and female patients of child-bearing potential were required to be using a reliable method of contraception. Fractures were ruled out based on the Ottawa ankle rules.[15] Patients subsequently noted to have grade III sprain or fracture were excluded from the study and referred for immediate care.

The exclusion criteria included pregnancy or breast-feeding, acute or chronic pain disorders, and current injury to both ankles or to both medial and lateral ligaments of the same ankle. Screened individuals were considered ineligible if they had any of the following in the sprained ankle: previous injury or surgery within the past 30 days, pain or instability due to a previous sprain or trauma, or ligament hyperlaxity due to connective tissue disease. Patients were also excluded if they had already used pain medications, massage, or physical therapy to treat the current ankle sprain (icing was permitted) or had current or past conditions or medication use that would preclude safe use of the study treatment or interfere with the validity of the study assessments.

Study outcomes

The primary outcome was the area under the curve (AUC) of PI on movement as measured on an 11-point NRS (described above) from 24 to 72 hours after the initial treatment application [i.e., days 1–3 (AUC_{1-3})]. The AUC_{1-3} was calculated based on the trapezoidal method as the sum of the AUCs of PI for the time intervals 24–36, 36–48, 48–60, and 60–72 hours. The secondary outcomes were the patient-reported PRS, time to onset of PR, time to meaningful PR, time to onset of a cooling sensation, time to complete recovery, PI difference (PID) on movement and at rest, sum of PI differences (SPID), total PR (TOTPAR), reduction in ankle swelling, and the patient's global assessment of their response to treatment.

The time to onset of PR was recorded as the time point at which the patients first reported a PRS of $\geq$1, representing ''a little'' or ''perceptible'' PR, confirmed by subsequent achievement of ''meaningful'' PR. The time to meaningful PR was defined as the first recording of a PRS of $\geq$2. The time to onset of cooling was defined as the time point at which the patients first endorsed experiencing a ''cooling effect as an enhancement of PR'' on the diary questionnaire. The time to complete recovery was the first day on which the patient reported complete relief of ankle pain and swelling. The PID on movement was calculated as $PID_t = PI_{baseline} - PI_{time\ t}$, where PI is PI on movement as measured using the NRS ratings at baseline and time t. PID at rest was calculated similarly using the NRS scores at rest. The SPID was calculated as $SPID_t = \Sigma(PID_t \times [time_t - time_{t-1}])$, where PID_t = PID at time t, $time_t$ = time t in hours, and $time_{t-1}$ = time at previous time point t; the SPID was reported for hours 24–72 (1–3 days) and 0–168 (0–7 days). The TOTPAR was calculated as the sum of the products of the PRS with a time interval from one time point to another: $TOTPAR_t = \Sigma(PRS_t \times [time_t - time_{t-1}])$, where PRS_t = PRS at time t, $time_t$ = time t in hours, and $time_{t-1}$ = time at previous time point. The TOTPAR was reported for hours 24–72 (1–3 days) and 0–168 (0–7 days). Treatment differences were calculated for reduction in ankle swelling, measured as the change

in the ankle perimeter from baseline to days 3 and 7, based on the investigator's "figure-of-eight" measurement. (Because not all patients were expected to require 10 days of treatment, the final measurement on day 10 was performed only to provide reassurance that the patient did not need further treatment or follow-up.)

Safety outcomes included frequency, severity, and the relationship between treatment and adverse events (AEs) and serious AEs. Safety was evaluated from the first visit through 6 (±1) days after treatment completion.

Statistical analyses

Safety was analyzed in all patients who were randomized and received any study medication. Efficacy was evaluated in the intent-to-treat (ITT) population, which comprised patients who were randomized, received treatment, and provided at least one post-baseline efficacy assessment. A sensitivity analysis for the primary and some secondary outcomes was performed in a per-protocol (PP) population that comprised patients who fully complied with all study procedures without major protocol violations.

The sample size was estimated based on the $SPID_{1–3}$ data because the AUC of PI on movement and the SPID are similar measures. Based on the clinical estimation of the performance of diclofenac from previous data,[16] the effect of the diclofenac/menthol gel was assumed to be 27.5% greater than that of placebo and to show a difference of about 1.7 (8.0 for the diclofenac/menthol formulation vs. 6.3 for placebo). A sample size of 360 patients in a ratio of 3:3:2:2 ($n = 108$ in the diclofenac/menthol group, $n = 108$ in the 1% diclofenac group, $n = 72$ in the menthol group, and $n = 72$ in the placebo group) was determined to have 80% power to detect a significant difference between diclofenac/menthol compared with placebo at the 0.05% alpha level. Accounting for a dropout rate of 10%, enrollment of 400 patients was planned.

The $AUC_{1–3}$, PRS, PID, SPID, TOTPAR, reduction in ankle swelling, and global assessment were analyzed using a mixed model analysis of covariance using SAS Proc Mixed (SAS Institute, Cary, NC, USA), with treatment and site as fixed effects and baseline PI as a covariate. As a sensitivity analysis, the mixed model analysis of covariance was repeated for the primary efficacy endpoint (AUC) with the site-by-treatment interaction effect added into the model. Differences among treatment least squares means for pairwise comparisons were performed at a 5% significance level ($P \leq 0.05$). The time to onset of PR, time to meaningful PR, time to a cooling sensation, and time to complete recovery were analyzed using a Cox proportional hazards model (PROC PHREG in SAS) with factors for treatments and baseline assessment of PI (NRS) and site as covariates. Summary statistics were calculated for all other endpoints.

For the $AUC_{1–3}$ and PRS, missing ratings during the first 3 days were imputed as the mean of the two adjacent values, if available. If all pain ratings or PR ratings were missing after a certain time point with no explanation, the patient was considered to have dropped out due to lack of efficacy, and subsequent pain rating scores were imputed using the last recorded score or the baseline score, whichever was more severe, and a score of 0 was assigned for the missing PRS. If a patient dropped out of the study because of an AE or reasons unrelated to the study medication, then the last recorded PI score and PRS were carried forward through day 3. For patients who used the rescue medication, all pain assessments within a 6-hour period after the rescue medication was taken were imputed as the last reported pain score before rescue medication use or the baseline pain score, whichever was worse; all PRSs during this time were set to 0. The procedure

was repeated as many times as the patient used the rescue medication.

Compliance was calculated for each patient as a percentage (number of gel applications recorded in the diary card divided by the number of planned applications). The number of planned applications was calculated as the number of days the patient remained in the study multiplied by 4. Overall compliance was calculated as the mean of the individual patients' compliance.

Results

Study population

In total, 385 patients met the enrollment criteria and were randomly assigned to treatment. The safety and ITT populations both comprised 381 patients, and 360 completed the trial (Figure 1). The ITT population included 117 patients in the diclofenac/menthol group, 112 in the 1% diclofenac group, 77 in the 3% menthol group, and 75 in the placebo treatment group. There were 341 patients with no major protocol violations who were included in the PP population. A total of 40 patients had protocol violations, including 16 with acute, chronic, or recurrent pain (in violation of the exclusion criteria), 14 with poor compliance, 4 who had taken medications likely to interfere with subjective assessments (again in violation of the exclusion criteria), 4 who dropped out of the study, 1 who used rescue medication for most of the study, 1 with medial distortion of the ankle, 1 who was misallocated to treatment, and 1 for whom drug screening was not performed. Although aspirin doses of 81 or 325 mg/day were permitted for cardiac prophylaxis based on the study protocol, none of the enrolled patients used aspirin for this indication during the study.

The baseline demographic characteristics and PI were similar across the treatment groups (Table 1). Mean compliance was 94% to 96% across all treatment arms. Rescue medication was used on one or more occasions by 20 (17.1%) patients in the 1% diclofenac/3% menthol gel group,

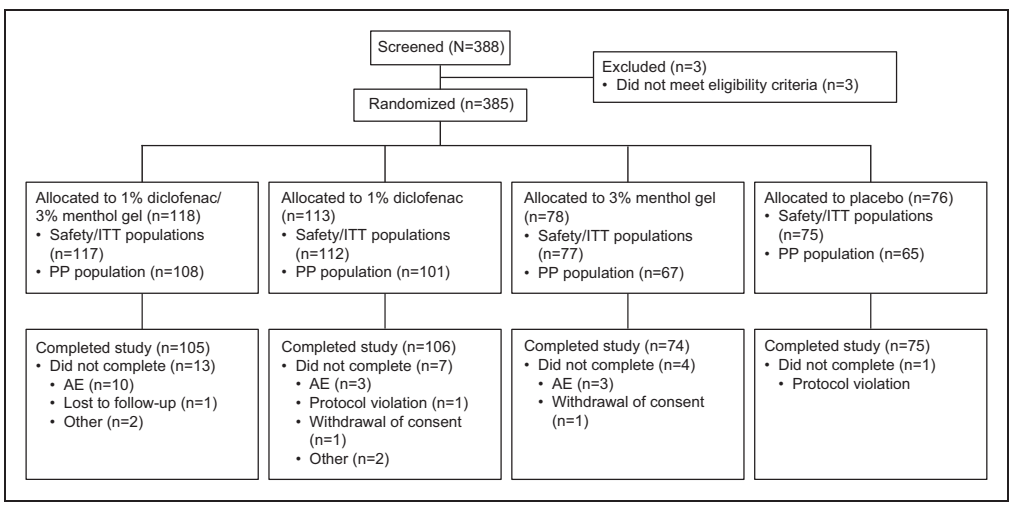

Figure 1. Patient flow.
[a]All patients who received at least one dose of medication also provided at least one post-baseline assessment; therefore, the safety and intent-to-treat populations were identical.

Table 1. Baseline demographics and pain intensity in the safety and intent-to-treat populations

	1% Diclofenac/3% menthol gel (n = 117)	1% Diclofenac gel (n = 112)	3% Menthol gel (n = 77)	Placebo gel (n = 75)
Sex, n (%)				
Male	67 (57.3)	71 (63.4)	38 (49.4)	40 (53.3)
Female	50 (42.7)	41 (36.6)	39 (50.6)	35 (46.7)
Race, n (%)				
White	115 (98.3)	111 (99.1)	74 (96.1)	75 (100.0)
Black	1 (0.9)	1 (0.9)	1 (1.3)	0 (0.0)
Asian	1 (0.9)	0 (0.0)	1 (1.3)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Age, years				
Mean (SD)	32.4 (11.8)	32.1 (11.4)	33.8 (12.2)	33.2 (11.6)
Median	30.0	29.5	32.0	32.0
Range	17–63	16–61	16–63	17–62
Pain intensity on movement[a]				
Mean (SD)	7.8 (1.6)	7.4 (1.4)	7.8 (1.6)	7.7 (1.5)
Median	8.0	8.0	8.0	8.0
Range	5–10	5–10	5–10	5–10
Duration of time between injury and baseline assessment, hours				
Mean (SD)	12.5 (7.0)	12.8 (6.6)	12.4 (7.2)	12.7 (6.9)
Median	14.0	15.0	14.3	14.9
Range	0.8–24.0	0.0–23.5	0.0–24.3	0.0–22.7

[a]Patients rated their pain intensity on movement (walking 5 steps on a flat surface) on a scale ranging from 0 = no pain to 10 = extreme pain.
SD, standard deviation.

17 (15.2%) in the 1% diclofenac gel group, 19 (24.7%) in the 3% menthol gel group, and 18 (24.0%) in the placebo group.

Efficacy

Table 2 shows results for the primary efficacy endpoint, $AUC_{1–3}$ for PI on movement. There was no statistically significant difference in pain reduction as measured by the adjusted mean $AUC_{1–3}$ between 1% diclofenac/3% menthol gel (261.43) and placebo (270.66), nor was there a statistically significant difference in this endpoint between 1% diclofenac/3% menthol gel and either of the active controls (1% diclofenac gel, 259.85; 3% menthol gel, 258.82). Furthermore, neither active control significantly differed from placebo on this endpoint. The results were similar for the sensitivity analysis that included the site-by-treatment interaction in the model.

There were no statistically significant differences in the PRS between 1% diclofenac/3% menthol gel and placebo or either active control at any time point from 10 minutes to 72 hours after the first treatment application (Figure 2). Mean PR was similar across all four treatment groups (Figure 2), and the active controls did not significantly improve the PRS compared with placebo at any time point. The other secondary efficacy outcomes (Tables 3 and 4) did not reveal any meaningful advantages for 1% diclofenac/3% menthol over placebo or either active control.

Table 2. AUC_{1-3} for pain intensity on movement with 1% diclofenac/3% menthol gel compared with 1% diclofenac gel, 3% menthol gel, and placebo gel in the intent-to-treat population

			Comparison with 1% diclofenac/3% menthol gel		
Treatment	N	Adjusted mean[a]	Treatment difference[b]	95% CI	*P*-value
1% diclofenac/3% menthol gel	117	261.43	–	–	–
1% diclofenac gel	112	259.85	1.58	−18.34, 21.50	0.8761
3% menthol gel	77	258.82	2.61	−19.46, 24.67	0.8164
Placebo gel	75	270.66	−9.23	−31.45, 12.98	0.4144

[a]Least squares treatment means from mixed model analysis of covariance, with treatment and site as fixed effects and pain intensity at baseline as a covariate. Lower values indicate a better response because of lower pain intensity over time.
[b]Difference in least squares means for the treatment named in each row minus the 1% diclofenac/3% menthol gel.
AUC_{1-3}, area under the curve of pain intensity on movement as measured on an 11-point numerical rating scale from 1 to 3 days after the initial treatment application; CI, confidence interval.

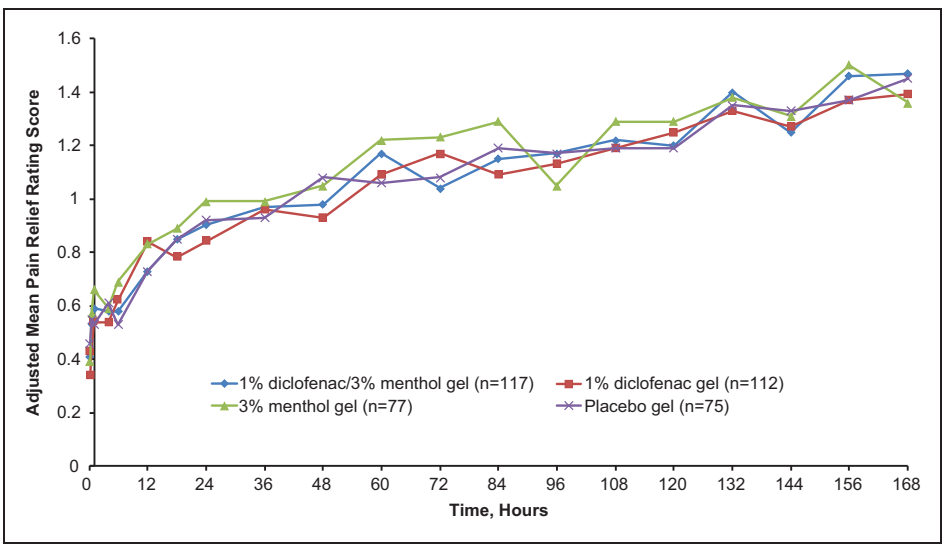

Figure 2. Adjusted mean pain relief ratings with 1% diclofenac/3% menthol gel compared with 1% diclofenac gel, 3% menthol gel, and placebo in the intent-to-treat population. Pain relief was assessed using a 5-point scale: 0 = no pain relief, 1 = a little or perceptible pain relief, 2 = meaningful pain relief, 3 = a lot of pain relief, and 4 = complete pain relief. The adjusted mean pain relief rating score is the least squares mean from the mixed model analysis of covariance, with treatment and site as fixed effects and pain intensity at baseline as a covariate.

Safety

The 1% diclofenac/3% menthol gel was associated with a greater number of treatment-emergent AEs (TEAEs) and treatment-related TEAEs compared with the other treatments; these TEAEs largely consisted of skin and application-site events (Table 5). Two patients, both in the 1% diclofenac/3% menthol arm, experienced

Table 3. Time-to-event outcomes in the intent-to-treat population

	1% Diclofenac/ 3% menthol gel (n = 117)	1% Diclofenac gel (n = 112)	3% Menthol gel (n = 77)	Placebo gel (n = 75)
Time to onset of pain relief in hours, median (range)	1.03 (0.2–157.0)	4.00 (0.2–168.0)	1.00 (0.2–9.4)	4.00 (0.2–187.5)
HR vs. placebo (95% CI)[a,b]	1.10 (0.81, 1.48)	1.00 (0.74, 1.36)	1.22 (0.88, 1.70)	—
Time to onset of meaningful pain relief in hours, median (range)	92.50 (0.2–203.8)	76.83 (0.2–184.1)	72.00 (0.2–203.5)	93.50 (0.2–203.0)
HR vs. placebo (95% CI)[a,b]	0.93 (0.67, 1.31)	0.93 (0.66, 1.31)	0.76 (0.52, 1.11)	—
Time to onset of cooling sensation in hours, median (range)	0.17 (0.2–6.0)	0.17 (0.2–6.0)	0.17 (0.2–6.0)	0.17 (0.2–6.0)
HR vs. placebo (95% CI)[a,b]	1.06 (0.79, 1.43)	0.99 (0.73, 1.34)	1.05 (0.76, 1.46)	—
Time to complete recovery in hours, median (range)	240.0 (17.0–240.0)	240.0 (48.2–240.0)	240.0 (53.2–240.0)	240.0 (145.5–240.0)
HR vs. placebo (95% CI)[a,b]	2.43 (1.04, 5.70)[c]	1.76 (0.73, 4.25)	1.86 (0.73, 4.72)	—

[a]Cox proportional hazard ratio and 95% confidence intervals of survival time (i.e., time to event).
[b]There were also no significant differences between 1% diclofenac/3% menthol gel and either active treatment (data not shown).
CI, confidence interval; HR, hazard ratio.

severe TEAEs. One patient developed application-site vesicles and necrosis, and the other had a hypersensitivity reaction; these events were considered treatment-related. All other TEAEs were mild or moderate. No serious AEs were reported.

Discussion

The primary and secondary efficacy endpoints were not met in this trial. There were no significant improvements in the primary and secondary endpoints for 1% diclofenac/3% menthol gel relative to placebo, 1% diclofenac gel, or 3% menthol gel. Treatment of acute ankle sprain with 1% diclofenac/3% menthol gel was associated with a greater likelihood of application site and skin TEAEs. To our knowledge, this is the only published study to have evaluated the efficacy and safety of a combination topical diclofenac and menthol analgesic.

In this study, the active control gel containing 1% diclofenac alone showed no significant PR compared with placebo. Other randomized controlled studies have demonstrated efficacy with topical diclofenac or other NSAIDs compared with placebo. In fact, a Cochrane meta-analysis of randomized double-blind active- or placebo-controlled trials in acute musculoskeletal pain concluded that there is moderate- to

Table 4. Assessments of pain, global response, and ankle swelling in the intent-to-treat population[a]

	1% Diclofenac/ 3% menthol gel (n = 117)	1% Diclofenac gel (n = 112)	3% Menthol gel (n = 77)	Placebo gel (n = 75)
PID on movement				
24 hours				
Mean (SD)	6.15 (2.27)	5.84 (2.08)	6.00 (2.49)	6.16 (2.14)
Difference vs. placebo (95% CI)[b]	−0.05 (−0.53, 0.43)	−0.07 (−0.55, 0.42)	−0.18 (−0.71, 0.34)	
P-value vs. placebo[c]	0.8274	0.7882	0.4973	
48 hours				
Mean (SD)	5.85 (2.45)	5.41 (2.10)	5.71 (2.67)	5.77 (2.44)
Difference vs. placebo (95% CI)[b]	0.00 (−0.51, 0.51)	−0.13 (−0.64, 0.38)	−0.10 (−0.66, 0.46)	
P-value vs. placebo[c]	0.9957	0.6238	0.7241	
72 hours				
Mean (SD)	5.22 (2.49)	5.00 (2.14)	5.21 (2.66)	5.41 (2.22)
Difference vs. placebo (95% CI)[b]	−0.28 (−0.81, 0.24)	−0.21 (−0.74, 0.32)	−0.24 (−0.82, 0.33)	
P-value vs. placebo[c]	0.2888	0.4288	0.4036	
PID at rest				
24 hours				
Mean (SD)	1.32 (1.58)	1.39 (1.45)	1.47 (1.54)	1.13 (1.71)
Difference vs. placebo (95% CI)[b]	0.16 (−0.24, 0.56)	0.31 (−0.09, 0.72)	0.25 (−0.19, 0.69)	
P-value vs. placebo[c]	0.4205	0.1252	0.2641	
48 hours				
Mean (SD)	1.43 (1.60)	1.53 (1.46)	1.51 (1.70)	1.45 (1.84)
Difference vs. placebo (95% CI)[b]	−0.02 (−0.45, 0.40)	0.15 (−0.28, 0.58)	−0.02 (−0.49, 0.45)	
P-value vs. placebo[c]	0.9123	0.4945	0.9378	
72 hours				
Mean (SD)	1.91 (1.78)	1.91 (1.55)	1.86 (1.78)	1.76 (1.97)
Difference vs. placebo (95% CI)[b]	0.17 (−0.28, 0.61)	0.26 (−0.19, 0.71)	0.02 (−0.47, 0.51)	
P-value vs. placebo[c]	0.4597	0.2584	0.9367	

(continued)

Table 4. Continued.

	1% Diclofenac/ 3% menthol gel (n = 117)	1% Diclofenac gel (n = 112)	3% Menthol gel (n = 77)	Placebo gel (n = 75)
SPID				
1–3 days				
Mean (SD)	101.54 (87.18)	100.07 (71.09)	104.26 (83.69)	90.88 (82.63)
Difference vs. placebo (95% CI)[b]	10.61 (−11.94, 33.16)	11.69 (−11.10, 34.48)	12.21 (−12.53, 36.96)	
P-value vs. placebo[c]	0.3556	0.3137	0.3324	
0–7 days				
Mean (SD)	451.12 (265.92)	452.44 (244.49)	464.96 (281.24)	438.45 (287.37)
Difference vs. placebo (95% CI)[b]	18.16 (−56.00, 92.32)	28.92 (−45.47, 103.31)	15.03 (−65.56, 95.61)	
P-value vs. placebo[c]	0.6303	0.4450	0.7140	
TOTPAR				
1–3 days				
Mean (SD)	44.10 (29.34)	45.11 (26.43)	47.84 (29.10)	43.04 (31.57)
Difference vs. placebo (95% CI)[b]	0.94 (−7.11, 9.00)	1.74 (−6.40, 9.89)	3.43 (−5.41, 12.28)	
P-value vs. placebo[c]	0.8179	0.6742	0.4457	
0–7 days				
Mean (SD)	172.97 (98.84)	170.73 (97.19)	184.17 (102.79)	174.00 (94.92)
Difference vs. placebo (95% CI)[b]	1.29 (−27.26, 29.84)	−0.28 (−28.98, 28.42)	4.90 (−26.11, 35.91)	
P-value vs. placebo[c]	0.9293	0.9846	0.7560	
Patient global assessment in response to treatment				
Day 10 (or end of treatment)				
Mean (SD)	2.20 (0.95)[d]	1.93 (1.05)	2.16 (1.04)	1.96 (1.08)
Difference vs. placebo (95% CI)[b]	0.23 (−0.05, 0.52)	−0.05 (−0.34, 0.24)	0.15 (−0.16, 0.47)	
P-value vs. placebo[c]	0.1114	0.7191	0.3451	
Reduction in ankle swelling, mm				
Day 3				
Mean (SD)	566.2 (57.0)	566.9 (49.6)	567.0 (56.5)	565.4 (52.7)
Difference vs. placebo (95% CI)[b]	−3.60 (−7.57, 0.37)	−4.15 (−8.16, −0.15)	−1.12 (−5.48, 3.25)	
P-value vs. placebo[c]	0.0755	0.0422	0.6154	

(continued)

Table 4. Continued.

	1% Diclofenac/ 3% menthol gel (n = 117)	1% Diclofenac gel (n = 112)	3% Menthol gel (n = 77)	Placebo gel (n = 75)
Day 7				
Mean (SD)	558.3 (56.0)	558.8 (46.4)	558.4 (56.9)	557.0 (50.9)
Difference vs. placebo (95% CI)[b]	−3.00 (−7.30, 1.30)	−2.59 (−6.92, 1.74)	−0.38 (−5.08, 4.32)	
P-value vs. placebo[c]	0.1706	0.2402	0.8741	

[a]n values shown in the column headings represent the full intent-to-treat population; sample sizes for the individual endpoints varied due to missing data at some time points for some outcomes.
[b]Difference in least squares means and 95% confidence intervals for each active treatment minus placebo.
[c]P-value for active treatments vs. placebo from multiple comparisons using *t*-test in Proc Mixed (SAS Institute); other between-group comparisons were not statistically significant unless otherwise noted.
[d]$P = 0.0300$ for diclofenac/menthol vs. diclofenac.
SD, standard deviation; CI, confidence interval; PID, pain intensity difference: TOTPAR, total pain relief; SPID, sum of pain intensity differences.

high-quality evidence that topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin all produce superior PR compared with topical placebo in acute conditions including strains, sprains, and other types of sports or overuse-related injuries, with diclofenac and ketoprofen being the most effective.[17]

Individual studies have demonstrated efficacy specifically of diclofenac gel in the treatment of acute ankle sprain.[18,19] In a phase III multicenter study conducted in Germany (NCT01272934), topical 1% diclofenac sodium gel applied four times daily was associated with less pain on movement at 72 hours compared with placebo (mean, 25.6 vs. 61.2 mm for placebo on a 100-mm visual analog scale [VAS]) and provided more rapid onset of PR (median, 4 hours vs. not achieved with placebo) in adult patients with acute grade I or II ankle sprain that had occurred within 12 hours of enrollment (N = 205).[18] Another randomized, double-blind study conducted at six centers in Germany evaluated a higher concentration diclofenac gel (2.32%) applied as 2 g rubbed into the ankle for about 1 minute, two or three times daily for 7 days in adults with acute grade I or II ankle sprain that had occurred within 12 hours of randomization (N = 242).[19] On day 5, the mean changes in the 100-mm VAS pain ratings were −49.1 and −49.7 mm with the diclofenac regimens, respectively, vs. −25.4 mm with placebo (both $P < 0.0001$).[19]

A 1.3% diclofenac epolamine topical patch[20] and a 4% diclofenac spray gel[21] have also shown efficacy over placebo in the treatment of acute ankle sprain. Effective relief of pain associated with acute ankle sprain has also been demonstrated with a variety of other topical NSAIDs, including 5% ibuprofen cream,[22] 2% ketorolac gel,[23] a 100-mg/day ketoprofen patch,[24] 2.5% niflumic acid gel,[25] and 0.2% mucopolysaccharide polysulphate/2% salicylic acid cream.[26] Topical 1% (or 1.16%) diclofenac gel also has shown efficacy over placebo in

Table 5. Treatment-emergent adverse events in the safety population

	1% Diclofenac/ 3% menthol gel (n = 117)	1% Diclofenac gel (n = 112)	3% Menthol gel (n = 77)	Placebo gel (n = 75)
Patients with ≥ 1 TEAE, n (%)	43 (36.8)	26 (23.2)	22 (28.6)	17 (22.7)
Number of TEAEs	80	37	41	20
Patients with treatment-related TEAEs, n (%)	40 (34.2)	23 (20.5)	18 (23.4)	9 (12.0)
Number of events	69	32	28	12
Patients with severe TEAEs, n (%)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Number of events	3	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs occurring in >3% of any treatment arm, n (%)				
General disorders and application-site conditions				
Application-site dryness	15 (12.8)	7 (6.3)	3 (3.9)	4 (5.3)
Application-site pain	7 (6.0)	0 (0.0)	2 (2.6)	1 (1.3)
Application-site pruritus	5 (4.3)	3 (2.7)	1 (1.3)	1 (1.3)
Application-site erythema	4 (3.4)	1 (0.9)	2 (2.6)	0 (0.0)
Skin and subcutaneous tissue disorders				
Dry skin	10 (8.5)	10 (8.9)	10 (13.0)	4 (5.3)
Pruritus	7 (6.0)	4 (3.6)	3 (3.9)	1 (1.3)
Erythema	6 (5.1)	2 (1.8)	3 (3.9)	1 (1.3)
Nervous system disorders				
Headache	4 (3.4)	2 (1.8)	4 (5.2)	3 (4.0)

TEAE, treatment-emergent adverse event.

relieving pain associated with osteoarthritis,[7,27–29] as well as acute neck pain,[30] in randomized, double-blind trials.

Our results differ from the body of literature documenting the efficacy of topically applied NSAIDs in an ankle sprain model of pain. Possible explanations may include differences in the pain scales used (11-point NRS vs. 100-mm VAS), the longer interval between injury and treatment in our study (up to 24 hours vs. 12 in the two above-mentioned German studies[18,19]), no stratification by time since injury, and possible differences in dosing frequency, dose volume, and time spent rubbing the product into the skin. Patients did not always comply with self-assessment time schedules or avoid prohibited medications, such that the ITT analysis included 40 patients with protocol violations. Nonetheless, the results in the PP population also failed to show a significant treatment effect for diclofenac/menthol gel vs. placebo. Because there is no objective measurement for pain, studies of analgesics must rely on subjective pain rating scales. The amount of rescue medication used, particularly in the menthol and placebo groups, may also have influenced the results. Finally, this study was conducted in patients with acute ankle sprain who tend to be physically active individuals; therefore, the results may not be generalizable to other populations with other types of musculoskeletal pain.

The combination of diclofenac and menthol resulted in increased reported local AEs compared with placebo or with diclofenac alone.

Conclusion

This study failed to show a statistically significant difference in the efficacy of topical 1% diclofenac/3% menthol gel

self-administered four times daily compared with placebo, 1% diclofenac gel, or 3% menthol gel in the treatment of pain related to ankle sprain. Although the product was generally well tolerated, combining topical 1% diclofenac with 3% menthol increased the incidence of mostly mild to moderate skin and application-site conditions compared with placebo or topical 1% diclofenac alone.

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Declaration of conflicting interest

Pamela Lai and Kenneth Reed are employees of GlaxoSmithKline Consumer Healthcare. Agron Collaku was an employee of GlaxoSmithKline Consumer Healthcare at the time of the study conduct and analysis.

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