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Topical pain relief cream formulation in the management of knee osteoarthritis: a randomized, double-blind and placebo-controlled clinical study

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ABSTRACT

Background: Topical formulations provide localized pain relief with improved safety profile. This study evaluated the efficacy and safety of a topical pain relief cream formulation in subjects with knee OA compared with placebo.
Methods: This multicentric, randomized, double-blind, placebo-controlled clinical study analyzed 335 subjects with clinically diagnosed knee OA who received either a topical pain relief cream formulation (Group B, n=166) or placebo (Group A, n=169) for 28 days. Primary efficacy endpoints were knee joint pain assessed using visual analog scale (VAS) and joint swelling. Secondary endpoints included modified Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, knee joint tenderness, warmth, onset and duration of action, global assessments, and safety.
Results: The topical pain relief cream formulation demonstrated significantly greater reductions in knee joint pain (19.7-21.4% at day 14 and 38.3-38.6% at day 28, $p<0.001$) and swelling ($p<0.001$) compared with placebo. Modified WOMAC scores for pain, stiffness, and difficulty in movements were also significantly ($p<0.05$) improved than placebo. The formulation demonstrated a significantly ($p<0.001$) faster onset and longer duration of action in terms of pain relief. Knee tenderness and rescue medication use were significantly ($p<0.05$) reduced. The formulation was well tolerated with no treatment-related adverse events (AEs).
Conclusions: The topical pain relief cream formulation significantly reduced knee joint pain and swelling while improving joint function. These findings support its potential as a safe, fast acting and effective topical therapy for managing knee OA.

Keywords: Topical pain relief cream formulation, Osteoarthritis, Joint pain, Joint swelling

INTRODUCTION

Osteoarthritis (OA) is a chronic, degenerative joint disorder and a leading cause of disability worldwide. This multifactorial, slowly progressive disease is characterized by destruction of the articular cartilage, subchondral bone alterations, occasional effusion, and varying degrees of local inflammation.[1,2] Joint inflammation symptoms include swelling, redness, warmth, pain, and stiffness, leading to restricted movement and tenderness. As of 2019, approximately 528 million people were living with OA, an increase of 113% since 1990 with knee joint being the most frequently affected site (365 million cases).[3,4] Risk factors predisposing to OA include obesity, age, repetitive joint use, female gender, genetics and prior joint injury.[5,6] Articular cartilage is a smooth, white tissue covering the ends of bones in synovial joints, enabling nearly frictionless movement. In OA, the equilibrium between

synthesis and degradation of cartilage is disrupted by overexpression of matrix metalloproteinases (MMPs) and other degradative enzymes, leading to progressive loss of collagen and proteoglycans. Consequently, the cartilage becomes disorganized, water content increases, and elasticity is lost, resulting in structural and functional deterioration of the joint.[7-10] In addition to nociceptive and neuropathic mechanisms, OA pain may also involve nociplastic pain, which arises from altered nociception without evident tissue or nerve damage.[11-13] Patients with OA frequently exhibit mixed pain phenotypes, and those with nociplastic pain features, similar to those observed in fibromyalgia, often experience heightened pain intensity and poorer treatment responses, making management more challenging.[14,15]

Pain control remains the primary therapeutic goal, achieved through both pharmacological and non-pharmacological measures. Long-term use of oral nonsteroidal anti-inflammatory drugs (NSAIDs) is limited by gastrointestinal, cardiovascular, and renal adverse effects.[9,10] Consequently, clinical guidelines recommend topical NSAIDs as a safer and effective first-line alternative, particularly in elderly populations.[16] Despite these options, many patients report suboptimal symptom control, prompting interest in complementary and alternative topical therapies.[17,18]

However, most of the marketed complementary and alternative topical preparations lack robust clinical evaluation. The objective of the current study was therefore to clinically evaluate the efficacy and safety of a topical pain relief cream formulation containing Gandhapura taila, *Boswellia serrata* extract, *Pinus sylvestris* taila, Pudina satva, and Katuvira extract in a multicentric, randomized, double-blind, placebo-controlled study in subjects with clinically diagnosed knee OA.

METHODS

Trial design

A randomized, double-blind, placebo-controlled, multi-centric, comparative, prospective clinical trial was designed and conducted across seven hospital sites in India, including Nashik, Navi Mumbai, Boradi, Pune, Vadodara, and Solapur between January 30, 2025, and March 24, 2025. The trial commenced at each site following approval from the respective institutional ethics committee and registration with the Clinical Trial Registry-India (CTRI/2024/11/076439; registered on November 8, 2024). The study was conducted, recorded, and reported in accordance with current good clinical practice-AYUSH (GCP-ASU) guidelines issued by the Ministry of AYUSH. The treatment duration was 28 days and included three visits namely, screening/baseline visit (day 0), visit 1 (Day 14), and end-of-study visit (day 28). Written informed consent was obtained from all participants before any study-related procedure. Eligible participants, as determined by inclusion and exclusion criteria, were randomized in a 1:1 ratio to receive either placebo (Group A) or the topical pain relief cream formulation (Group B).

Participants were instructed to apply a thin layer of the assigned product (Group A or B) to the affected knee joint three times daily for 28 days. At each visit (Days 0, 14, and 28), participants underwent physical examination (height, weight and BMI) and vital sign assessment (pulse, respiratory rate, blood pressure, and temperature). Joint pain, swelling, warmth, and tenderness were evaluated at each visit. Compliance was assessed by the investigator during follow-up visits and AEs monitored throughout the study. At the end of the study (Day 28), both the participant's and investigator's global evaluations of overall improvement were recorded.

Participants

Male and female participants aged 30-65 years (inclusive) with clinically diagnosed knee pain due to OA with knee joint pain scoring between 30 and 70 (inclusive) on the visual analogue scale (VAS) were enrolled after obtaining written informed consent. Participants were excluded if they had chronic severe OA; other major joint diseases; history of surgery (including arthroscopy) or major trauma to the study joint; use of systemic corticosteroids within one month prior to screening; or any other investigational drug within one month prior to randomization. Other exclusion criteria included uncontrolled diabetes mellitus or hypertension; or any condition considered unsuitable by the investigator. Participants were permitted to use oral painkillers as rescue medication for breakthrough pain, and such use was recorded in the case report form (CRF).

Interventions

The investigational topical pain relief cream formulation contained Gandhapura taila (10% w/w), *Boswellia serrata* extract (1.5% w/w), *Pinus sylvestris* taila (0.5% w/w), *Pudina Satva* (5.5% w/w), and Katuvira extract (0.015% w/w). The placebo formulation was identical in appearance, color, and odor to the investigational product but without active ingredients. Both products were manufactured in compliance with good manufacturing practices (GMP) applicable to Ayurvedic formulations in India. Participants were instructed to apply a thin layer of the assigned product to the affected knee joint three times daily for 28 days.

Outcomes

Primary outcomes included reduction in knee joint pain and swelling from baseline to day 28 within and between groups. Knee joint pain was assessed using the 100 mm VAS.[19] Participants marked their perceived pain intensity on the horizontal VAS. Higher scores indicated greater pain intensity. Joint swelling was evaluated by measuring knee circumference (in cm) at three levels: mid-patella, 5 cm above the upper patellar border, and 5 cm below the

lower patellar border. Assessments for knee joint pain and swelling were performed during the baseline visit, visit 1 (day 14), and visit 2 (day 28).[20]

Secondary outcomes included reduction in pain, stiffness, and physical function; reduction in knee joint tenderness and warmth; time of onset and duration of action from baseline to the end of the study visit (Day 28) within groups and comparison between the two groups; global assessment (by investigator and participant) for overall reduction in OA at the end of 28 days of study treatment and safety assessments including monitoring AEs, changes in vital signs; and global assessment of tolerability.

Modified WOMAC index (Center for rheumatic diseases, pune version) was used for the assessing pain, stiffness and physical function.[21] The WOMAC Index is a self-administered questionnaire with 24 items divided into 3 subscales, viz., pain (5 items), stiffness (2 items) and physical function (17 items) with each item rated from 0 to 4 corresponding to None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4). Higher scores indicate greater impairment. Knee joint tenderness[22] was assessed by firm pressure over the joint margin and scored on a 4-point scale (0=no tenderness, 1=patient complained of pain, 2=patient complained of pain and winced, 3=patient complained of pain, winced, and withdrew the joint). Modified WOMAC, knee joint tenderness and warmth [dichotomously as absent (0) or present (1)] were all assessed at baseline visit, days 14 and 28.[23] Time of onset and duration of action were noted in seconds/minutes/hours after application during the baseline visit. The Clinical global impression-improvement (CGI-I) scale was used by the investigator to assess overall improvement, rated on a 7-point scale from 1 ("very much improved") to 7 ("very much worse"). Both investigators and participants provided global assessments at day 28.[24]

AEs were monitored at each follow-up visit. Vital signs including pulse rate, respiratory rate, blood pressure, and body temperature were evaluated at baseline, day 14, and day 28. The global assessment tolerability of study products by investigator and participants was evaluated on following safety grades with 1=excellent overall safety (no adverse drug reaction reported), 2=good overall safety (mild adverse drug reaction(s) reported which subsided with or without medication), 3=fair overall safety (moderate to severe adverse drug reaction reported which subsided with or without medication and did not necessitate stoppage of study treatment), and 4=poor overall safety (severe or serious adverse drug reaction reported which necessitated stoppage of study) on day 28. Number of subjects requiring rescue medication was compared between visits and between groups.

Sample size, randomization, and blinding

A total of 345 participants were enrolled, considering an anticipated 15% dropout rate, with 174 participants in group A (Placebo) and 171 in group B (Topical Pain Relief Cream Formulation).[25] Participants were randomized to the two groups in a 1:1 ratio using a computer-generated randomization list. Both investigators and participants were blinded to treatment allocation throughout the study.

Statistical methods

All the participants who completed the study as per the protocol were considered as "per protocol population". Also, all cases who took at least one dose of the study drug were considered as "Safety population" and were evaluated accordingly. Knee pain (VAS), joint swelling, and modified WOMAC index scores were analyzed using Wilcoxon signed-rank test for within-group comparisons and Mann-Whitney U test for between-group comparisons. The paired and unpaired Student's t-tests were used to analyses the mean time of onset and duration of action. Categorical variables, including global assessment ratings, were analyzed using the Chi-square test or Fisher's exact test when expected cell frequencies were <5. AEs were summarized by number of events and number of affected participants. Vital sign changes were analyzed using the student's t test. All analyses were performed using standard statistical software, and $p \leq 0.05$ (two-sided) was considered statistically significant.

RESULTS

Participants flow

A total of 345 eligible participants were randomized in a 1:1 ratio into two group A (n=174, received placebo) and group B (n=171, received the topical pain relief cream formulation). Ten subjects (5 in each group) were lost to follow-up and considered dropouts. Finally, 335 participants (Group A: 169 and group B: 166) completed the study and were analyzed for efficacy (Figure 1). Safety analysis included subjects who received at least one dose of the study product.

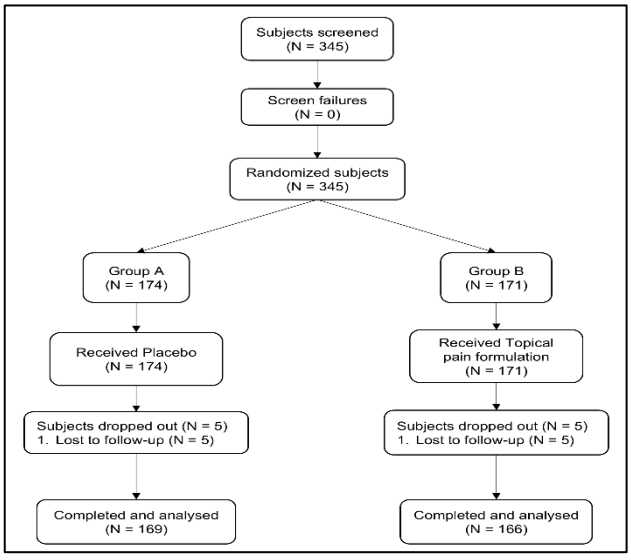

Figure 1: Participants flow.

Baseline characteristics

The demographic characteristics (Table 1) were comparable between the two groups, with no statistically significant differences ($p>0.05$ for all parameters). The mean age of participants was 49.49±9.40 and 49.28±9.46 years in group A and B ($p=0.838$), respectively. Group A comprised 47 males (27.8%) and 122 females (72.2%), while group B comprised 35 males (21.1%) and 131 females (78.9%) ($p=0.152$). Mean body weight was 63.28±11.65 kg in group A and 63.43±11.94 kg in group B ($p=0.907$). Corresponding mean BMI values were 25.83±4.31 kg/m² and 26.17±5.05 kg/m² for groups A and B, respectively ($p=0.508$).

Knee joint pain

At baseline, there was no statistically significant difference in right knee joint pain VAS scores between group A (53.98±12.29, n=103) and group B (55.10±11.14, n=103) ($p>0.05$). At both days 14 and 28, significant reductions ($p=0.001$) in VAS scores were observed in both groups compared with their respective baselines. However, the magnitude of reduction was significantly greater in group B compared with group A at both time points ($p=0.001$ between groups). Similar trends were observed for the left knee joint, where group B (n=63) demonstrated a significantly greater improvement in pain reduction compared with group A (n=66) (Figure 2).

At day 14, the mean percentage reduction in right knee pain was 12.1% in the placebo group (Group A) and 19.7% in the topical pain relief cream formulation group (Group B). By day 28, these reductions increased to 21.7% and 38.6%, respectively. Similarly, for the left knee joint, the mean percentage reduction from baseline at day 14 was 10.6% in group A and 21.4% in group B, which further improved to 19.3% and 38.3%, respectively, at day 28 (Table 1). Overall, the topical pain relief cream formulation (Group B) demonstrated approximately 17 to 19 points better pain relief in knee pain within 4 weeks compared to placebo (Group A), corresponding to nearly two-fold higher percentage improvement from baseline.

Knee joint swelling

At baseline, the mean circumferences of both right and left knees were comparable between the two groups (Figure 3-5). By day 14, reductions in joint circumference were observed at all measured points in both groups, but statistical significance within groups ($p\leq0.05$) was seen primarily in group B and only at selected sites in the Group A. The between-group differences were significant ($p\leq0.05$) at all anatomical locations. By day 28, both groups showed further reductions in knee circumference compared to baseline. However, the reduction was consistently more pronounced and statistically significant ($p<0.05$) in group B across all sites namely mid-patellar (Figure 3), 5 cm above (Figure 4), and 5 cm below (Figure 5) the patella for both knees with some instances of visible reduction in swelling. Group A also showed mild but statistically significant reductions at several measurement points, though of lesser magnitude than group B. For example, at right mid-patellar level, mean circumference decreased from 37.99±4.37 cm at baseline to 37.43±4.32 cm at day 28 in group B, compared with 37.83±4.20 cm to 37.54±4.16 cm in A. Similar trends were observed at 5 cm above and below the patellar borders and for left knee.

By day 14, the group A demonstrated marginal reductions in knee circumference ranging from 0.23% to 0.46%, whereas the group B showed greater reductions ranging from 0.71% to 1.94% across all measurement points. At day 28, the improvement became more pronounced in both groups, but the extent of reduction in group B was consistently higher from 1.19% to 2.84%, compared with 0.34% to 0.88% in group A (Table 1). The largest improvement was observed at 5 cm below the left knee patellar border, where swelling reduced by 2.84% in the group B versus 0.49% in the group A.

Secondary efficacy outcomes

The analysis of secondary endpoints (Table 2) further supported the superior efficacy of the group B compared to the group A in reducing pain, stiffness, and improving physical function, and overall clinical condition in subjects with OA of the knee.

Modified WOMAC scores

At baseline, mean WOMAC subscores for pain, stiffness, and physical difficulty in movement were comparable between both groups for both knees. Significant reductions were observed in all subscales over the 28-day period, with group B demonstrating significantly greater improvements than placebo ($p<0.05$ between groups) (Table 2). In the right knee, pain scores decreased from 8.80±3.99 at baseline to 5.08±2.63 (42.3% reduction, $p=0.001$) on day 28 in group B, compared with a decrease from 8.82±3.03 to 7.32±2.57 (17.0% reduction, $p=0.001$) in group A ($p=0.001$). Similar trends were noted in the left knee, where group B exhibited a 42.8% reduction (from 9.44±3.54 to 5.40±2.25, $p=0.001$) versus 15.8% ($p=0.001$) in the group A ($p=0.001$) on day 28, indicating approximately 2.5 times better pain reduction in pain scores in 4 weeks with the topical pain relief cream formulation. A significant decline was noted in stiffness score among subjects treated in the group B. For the right knee, stiffness reduced from 3.64±2.14 to 2.50±2.01 (31.3% reduction, $p=0.001$) on day 28, while the group A showed no consistent trend. Similar trends were noted in the left knee, where group B exhibited a 35.6% reduction (from 3.57±1.86 to 2.30±1.67, $p=0.001$) versus 18.8% ($p=0.001$) in the group A ($p=0.004$) on day 28, indicating better reduction in morning stiffness in 4 weeks with the topical pain relief cream formulation. Functional improvement as assessed from the difficulty score was more pronounced in group B, with right knee scores declining from 30.71±11.42 to 15.23±5.98 (50.4%

reduction, p=0.001) and left knee scores from 32.81±10.67 to 16.98±5.48 (48.2% reduction, p=0.001) by day 28.

In contrast, the group A showed significantly lesser improvements [16.7% reduction in right knee, (p=0.001) and 16.9% reduction in the left knee, (p=0.001)], indicating approximately 3 times improvement in joint movements in 4 weeks with the topical pain relief cream formulation. By day 28, group B recorded a total WOMAC score of 22.82±8.68 (47.1% reduction, p=0.001) for the right knee and 24.75±7.62 (46.0% reduction, p=0.001) for the left knee, representing significantly (p=0.001) greater improvement compared to group A [36.08±13.81 (15.4% reduction) and 39.45±17.41 (17.2% reduction), respectively], indicating approximately 3 times better improvement in overall joint functionality with the topical pain relief cream formulation.

Tenderness and warmth

Tenderness declined from baseline in both groups; however, the reduction was significant at day 14 ($p<0.05$) and at day 28 ($p<0.001$) in group B (Table 2). The proportion of subjects reporting no tenderness increased from 25.3% (42 out of 166) at baseline to 36.1% (60 out of 166 subjects) at day 14 and 40.4% (19 out of 166 subjects) at day 28 in group B is better compared to the increase from 26% (44 out of 169, at baseline) to 33.1% (56 out of 169 subjects) at day 14 and 35.5% (60 out of 169 subjects) at day 28 in group A. Furthermore, the proportion of subjects reporting pain and winced decreased substantially from 38% (63 out of 166 subjects) at baseline to 11.5% (19 out of 166 subjects) at day 14 and 3% (5 out of 166 subjects) at day 28 in group B is better compared to 26.6% (45 out of 169 subjects) at day 14 and 17.8% (30 out of 169 subjects) decrease at day 28 in the placebo group. Warmth around the joint at day 28 was also reduced more in group B (from 32.5% to 27.7%) than in group A (from 32.5% to 34.9%) (Table 2).

Onset of action, duration of action and rescue medication usage

The onset of action in terms of pain relief in the group B was within 1.5 minutes (97.23±76.77 s), which was significantly (p=0.001) faster than group A (160±122.02 s), and the duration of action in terms of pain relief was approximately three times longer (90.38±49.18 minutes vs 30.16±18.18 minutes, p=0.001), indicating the long-lasting pain relief. Use of rescue medication was significantly (p=0.001) lower in the group B, with only 6.6% of subjects requiring additional analgesics on days 14 and 28, compared to ~18% in the group A (Table 2), indicating the reduced need of rescue medication with the topical pain relief cream formulation.

Global assessment

Both investigator and participant global assessments showed significantly substantial differences favoring the group B. By day 28, 71.1% of participants in group B were rated as much or very much improved by investigators, compared to 26% in the group A (p=0.001).

Similarly, 70.5% of participants in grp B self-rated as much/ very much improved, vs 27.3% in A (p=0.001) (Table 2). Overall, approximately 3× better improvement observed with topical pain relief cream formulation as assessed by both investigator and by participants.

Safety outcomes

Both the topical pain relief cream formulation (Group B) and placebo (Group A) were well tolerated throughout the 28-day study period, with no clinically significant changes in vital signs or systemic safety parameters in either group (Table 2).

Global assessment of tolerability

At Day 28, overall tolerability assessed by both investigators and participants was rated higher in the group B than in the group A. In the investigator assessment, "Excellent" safety was reported in 54.8% of group B participants compared with 45.6% in group A (p=0.001), while "Good" tolerability was reported in 36.1% versus 31.4% (p=0.001), respectively. Only 1.2% of participants in group B were rated as having "Poor" tolerability compared with 3.5% in group A. In the participant assessment, consistent with investigator findings, 55.4% of participants in group B (p=0.001) and 45.6% in group A rated the formulation as "Excellent" in safety, while 37.3% (p=0.001) and 32.0%, respectively, rated it as "Good." Reports of "Fair" or "Poor" tolerability were minimal, accounting for only 7.2% in group B compared with 22.5% in group A (Table 2). Thus, the topical pain relief cream formulation is gentle on skin and well tolerated.

Vital signs

No clinically significant alterations were observed in pulse rate, respiratory rate, body temperature, or blood pressure across visits in either group. Mean values for pulse and respiratory rate remained within the normal physiological range throughout the study. Body temperature showed negligible changes from baseline to day 28, with final mean values of 97.52±0.85°F in group B and 97.60±0.80°F in group A. Systolic and diastolic blood pressures remained stable over time, with no clinically meaningful variations from baseline (Table 2).

AEs

A total of 52 AEs were reported during the study with 26 events each in the group A and B. The overall incidence of subjects reporting at least one AE was comparable between 2 groups, occurring in 12.4% (21/169) of participants in group A and 12.0% (20/166) in group B. Majority of reported events were mild and transient, with no serious or treatment-related AEs observed. Most commonly reported

AEs in both groups were cold, fever and cough, accounting for approximately half of all recorded events. Specifically, cold was reported by 4.1% of subjects in group A and 3.6% in B, followed by fever (1.8% vs. 2.4%) and cough (2.4% vs. 1.8%). Few subjects reported headache, gastrointestinal discomfort (abdominal pain, flatulence, dyspepsia)/minor dermatological complaints such as itching and xerosis, but these events were infrequent and self-limiting. Mild oedema, vomiting, and loose motion were each reported by 1 subject (0.6%) in group B, while constipation, acidity, eye redness, and throat pain occurred only in isolated cases within placebo group. Importantly, no serious AEs (SAEs)/treatment discontinuations were attributed to the study formulation. Overall, pattern and frequency of AEs similar between groups, indicating that topical pain relief cream formulation was safe and well tolerated, with no clinically significant safety concerns over 28-day treatment period (Table 3).

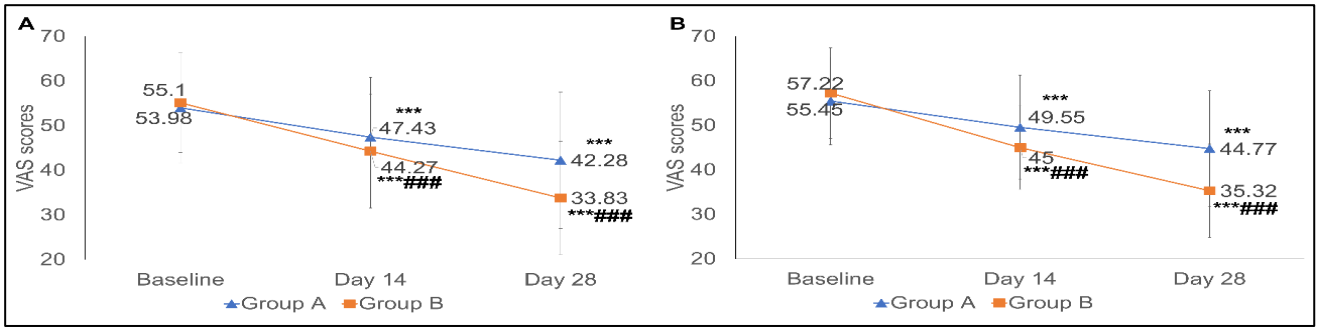

Figure 2: Effect of topical pain relief cream formulation on knee joint pain.

*A-Right knee joint; B-Left knee joint; grp A-Placebo; group B-Test formulation; ***p<0.005 vs baseline within same group; ###p<0.005 vs placebo (between groups); each value represents mean±SD (Right knee joint, n=103 for both groups; Left knee joint, n=66 for grp A and n=63 for B). Wilcoxon signed-rank test for within-group comparisons and Mann-Whitney U test for between-group comparisons.

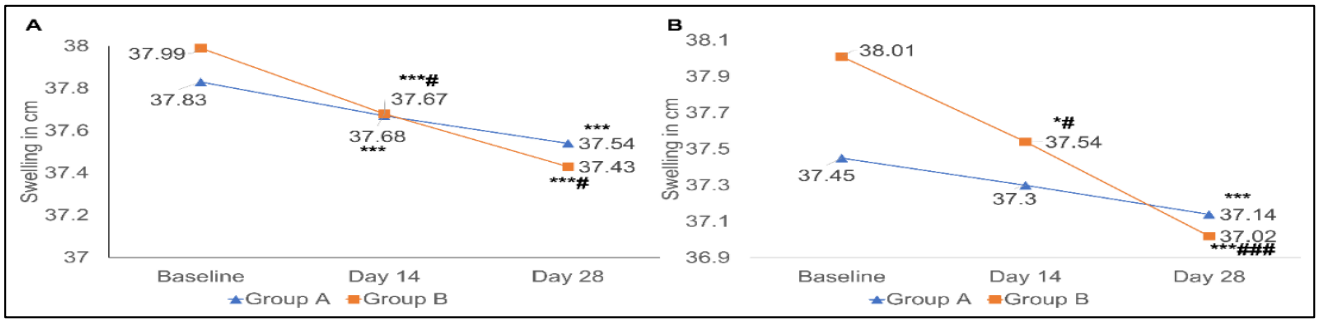

Figure 3: Effect of topical pain relief cream formulation on knee joint swelling at mid-patellar level.

*A-Right knee joint; B-Left knee joint; group A-Placebo; group B-Test formulation; *p≤0.05 and ***p<0.005 vs baseline within same group; #p≤0.05 and ###p<0.005 vs placebo (between groups); each value represents mean±SD (Right knee joint, n=103 for both groups; left knee joint, n=66 for grp A and n=63 for B). Wilcoxon signed-rank test for within-group comparisons and Mann-Whitney U test for between-group comparisons.

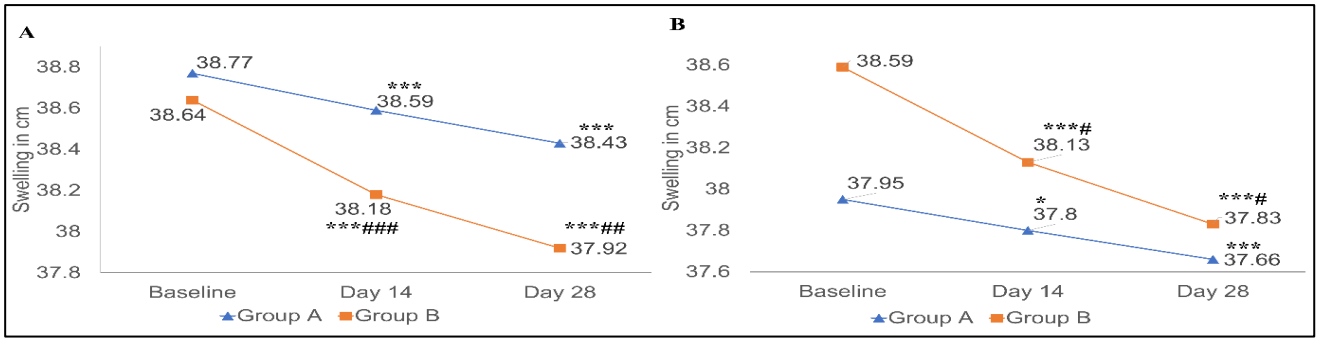

Figure 4: Effect of topical pain relief cream formulation on knee joint swelling at 5 cm above upper patellar border.

*A-Right knee joint; B-left knee joint; group A-Placebo; group B-Test formulation; *p≤0.05 and ***p<0.005 vs baseline within the same group; #p≤0.05, ##p<0.01 and ###p<0.005 vs placebo (between groups); each value represents mean±SD (Right knee joint, n=103 for both the groups; Left knee joint, n=66 for group A and n=63 for group B). Wilcoxon signed-rank test for within-group comparisons and Mann-Whitney U test for between-group comparisons.

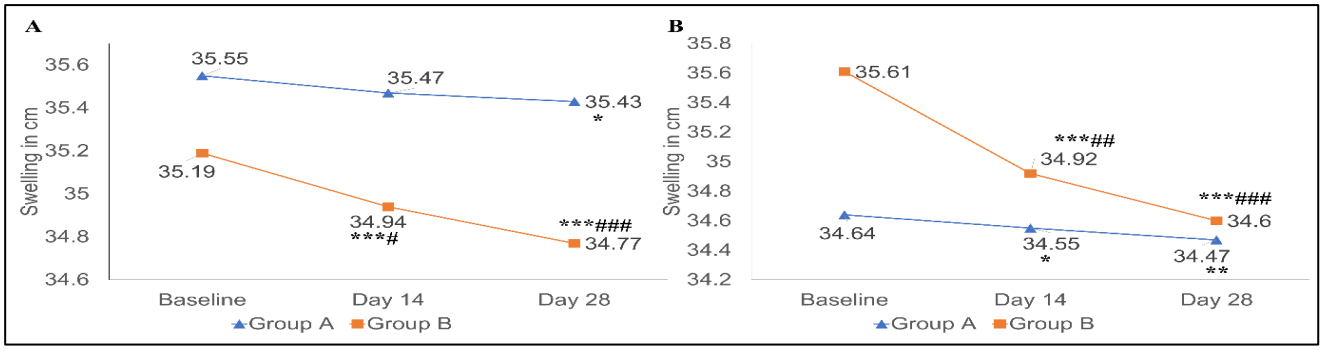

Figure 5: Effect of topical pain relief cream formulation on knee joint swelling at 5 cm below lower patellar border.
*A-Right knee joint; B-Left knee joint; group A-Placebo; group B-test formulation; *p≤0.05, **p<0.01 and ***p<0.005 vs baseline within the same group; #p≤0.05, ##p<0.01 and ###p<0.005 vs placebo (between groups); each value represents mean±SD (Right knee joint, n=103 for both the groups; left knee joint, n=66 for group A and n=63 for group B). Wilcoxon signed-rank test for within-group comparisons and Mann-Whitney U test for between-group comparisons.

Table 1: Percentage reduction in knee joint pain and swelling from baseline.

Primary efficacy parameters	Subjects/visits	Group A, (n=169)	Group B, (n=166)
Knee joint pain (VAS scores)			
Right knee pain (% reduction)	N	103	103
	Day 14	12.1%	19.7%
	Day 28	21.7%	38.6%
Left knee pain (% reduction)	N	66	63
	Day 14	10.6%	21.4%
	Day 28	19.3%	38.3%
Knee joint swelling			
Right knee at mid-patella	N	103	103
	Day 14	0.42%	0.82%
	Day 28	0.77%	1.47%
Left knee at mid-patella	N	66	63
	Day 14	0.40%	1.24%
	Day 28	0.83%	2.60%
Right knee at 5 cm above the upper patellar border	N	103	103
	Day 14	0.46%	1.19%
	Day 28	0.88%	1.86%
Left knee at 5 cm above the upper patellar border	N	66	63
	Day 14	0.40%	1.19%
	Day 28	0.76%	1.97%
Right knee at 5 cm below the lower patellar border	N	103	103
	Day 14	0.23%	0.71%
	Day 28	0.34%	1.19%
Left knee at 5 cm below the lower patellar border	N	66	63
	Day 14	0.26%	1.94%
	Day 28	0.49%	2.84%

*Grp A-Placebo; grp B-Test formulation; N-No. of subjects in grp; n=number of subjects with knee joint pain/swelling within each grp.

Table 2: Effect of topical pain relief cream formulation on secondary efficacy parameters.

Secondary outcomes	Subjects or visits	Group A, (n=169)	Group B, (n=166)
Modified WOMAC-pain score			
Right knee	N	103	103
	Baseline	8.82±3.03	8.80±3.99
	Day 14	7.80±2.53***	6.17±2.57***###
	Day 28	7.32±2.57***	5.08±2.63***###
Left knee	N	66	63
	Baseline	10.02±3.90	9.44±3.54
	Day 14	8.76±3.97***	7.76±2.98***###
	Day 28	8.44±3.95***	5.40±2.25***###

Continued.

Secondary outcomes	Subjects or visits	Group A, (n=169)	Group B, (n=166)
Modified WOMAC-stiffness score			
Right knee	N	103	103
	Baseline	3.14±1.90	3.64±2.14
	Day 14	2.85±1.83***	2.92±2.10***###
	Day 28	3.16±1.82	2.50±2.01***###
Left knee	N	66	63
	Baseline	3.62±1.86	3.57±1.86
	Day 14	3.05±1.79***	2.59±1.73***#
	Day 28	2.94±1.76***	2.30±1.67***###
Modified WOMAC-difficulty score			
Right knee	N	103	103
	Baseline	30.72±12.39	30.71±11.42
	Day 14	27.60±11.01***	20.61±8.05***###
	Day 28	25.60±11.02***	15.23±5.98***###
Left knee	N	66	63
	Baseline	34.03±13.94	32.81±10.67
	Day 14	28.61±13.21***	19.73±6.58***###
	Day 28	28.29±12.91***	16.98±5.48***###
Modified WOMAC-total score			
Right knee	N	103	103
	Baseline	42.67±16.04	43.15±15.96
	Day 14	38.25±14.17***	29.70±10.57***###
	Day 28	36.08±13.81***	22.82±8.68***###
Left knee	N	66	63
	Baseline	47.67±18.59	45.83±14.05
	Day 14	40.41±17.93***	30.68±8.68***###
	Day 28	39.45±17.41***	24.75±7.62***###
Tenderness			
No tenderness	Baseline	44 (26%)	42 (25.3%)
	Day 14	56 (33.1%)	60 (36.1%)*
	Day 28	60 (35.5%)	67 (40.4%)***
Patients complained of pain	Baseline	67 (39.6%)	58 (34.9%)
	Day 14	67 (39.6%)	87 (52.4%)
	Day 28	78 (46.1%)	94 (56.6%)
Patients complained of pain and winced	Baseline	54 (32%)	63 (38%)
	Day 14	45 (26.6%)	19 (11.5%)
	Day 28	30 (17.8%)	5 (3%)
Patients complained of pain, winced, and withdrew the joint	Baseline	4 (2.4%)	3 (1.8%)
	Day 14	1 (0.6%)	0 (0%)
	Day 28	1 (0.6%)	0 (0%)
Warmth			
Present	Baseline	55 (32.5%)	54 (32.5%)
	Day 14	54 (32%)	50 (30.1%)
	Day 28	59 (34.9%)	46 (27.7%)
Absent	Baseline	114 (67.5%)	112 (67.5%)
	Day 14	115 (68%)	116 (69.9%)
	Day 28	110 (65.1%)	120 (72.3%)
Onset of action (seconds)	Day 1	160±122.02	97.23±76.77###
Duration of action (minutes)	Day 1	30.16±18.18	90.38±49.18###
Rescue medications	Day 14	31 (18.3%)	11 (6.6%)###
	Day 28	30 (17.8%)	11 (6.6%)###
Global assessment for overall reduction in OA by investigator			
Very much improved	Day 28	7 (4.1%)	26 (15.7%)###
Much improved	Day 28	37 (21.9%)	92 (55.4%)###
Minimally improved	Day 28	69 (40.8%)	41 (24.70%
No reduction	Day 28	55 (32.5%)	6 (3.6%)
Minimally worse	Day 28	1 (0.6%)	1 (0.6%)
Global assessment for overall reduction in OA by participants (N, %)			
Very much improved	Day 28	6 (3.6%)	26 (15.7%)###
Much improved	Day 28	40 (23.7%)	91 (54.8%)###

Continued.

Secondary outcomes	Subjects or visits	Group A, (n=169)	Group B, (n=166)
Minimally improved	Day 28	62 (36.7%)	44 (26.5%)
No reduction	Day 28	59 (34.9%)	4 (2.4%)
Minimally worse	Day 28	2 (1.2%)	1 (0.6%)

*Group A-Placebo; group B-test formulation; *p<0.05 and ***p<0.005 vs baseline within the same group; ###p<0.05 vs placebo (between groups); values other than numbers and percentages represents mean±SD; N=Number of subjects in each group; n=number of subjects with affected knee within each group modified WOMAC index scores were analyzed using Wilcoxon signed-rank test for within-group comparisons and Mann-Whitney U test for between-group comparisons. The paired and unpaired Student's t tests were used to analyses the mean time of onset and duration of action. Between-group comparisons at each visit for tenderness were performed using 2×2 Chi-square test (No tenderness vs pain). Other categorical variables, including global assessment ratings, were analyzed using the Chi-square test or Fisher's exact test when expected cell frequencies were <5.

DISCUSSION

The present multicentric randomized, double-blind, placebo-controlled clinical study evaluated the efficacy and safety of a topical pain relief cream formulation in adults with knee OA. Participants who received the topical pain relief cream formulation (Group B) showed a marked and consistent reduction in pain intensity, as measured by the VAS in 4 weeks. By day 28, pain reduction reached approximately 38.6% in the right knee and 38.3% in the left knee, compared with 21.7% and 19.3%, respectively, in the placebo group. These findings confirm that the formulation produced clinically meaningful pain relief, corresponding to nearly two-fold higher percentage improvement from baseline beyond placebo effects. Similarly, reductions in knee joint swelling were observed at all measured sites (mid-patella, 5 cm above, and 5 cm below the patellar border). Although the magnitude of reduction was modest (0.7-2.8%), the consistent and statistically significant improvements in group B compared with group A suggest a localized analgesic and anti-inflammatory effect of the topical pain relief cream formulation, consistent with expected pharmacodynamic action of its botanical and natural constituents.

The modified WOMAC assessments further supported these results. The study formulation group demonstrated significant improvement across all domains like pain, stiffness, and difficulty in movement, resulting in a notable decrease in total WOMAC scores from baseline to day 28, which was 3 times better improvement in overall joint functionality than placebo. Improvements in functional parameters such as stiffness and difficulty performing daily activities underscore the holistic symptom relief provided by the treatment, extending beyond mere pain control. Additionally, tenderness grading and global assessments by both investigators and participants revealed a greater proportion of subjects reporting "much improved" or "very much improved" outcomes in the formulation group, further validating its perceived and clinically assessed benefits. The significantly lower need for rescue medication, faster onset of action, and longer duration of effect in Group B emphasize the formulation's rapid (in approximately 1.5 minutes) and long-lasting therapeutic response. The topical pain relief cream formulation was gentle on skin, better tolerated, with no serious or study-related AEs. The incidence and nature of AEs were comparable between groups, primarily comprising mild, self-limiting conditions such as cold, cough, or transient headache. Both investigators and participants rated tolerability as "excellent" in over 90% of cases in the treatment group. Vital signs and physiological parameters remained stable throughout the study, confirming the systemic safety of the formulation.

The therapeutic effects observed may be attributed to the active ingredients in the topical pain relief cream formulation. For example, *Gandhapura taila* (Gaultheria oil) containing methyl salicylate has long been utilized in traditional medicine for inflammation conditions such as arthritis.[26,27] A liniment containing methyl salicylate and menthol showed significant pain-reliving effects in a multicenter real-world study.[17] A topical *Boswellia* formulation enriched with boswellic acids significantly decreased pain and improved function in knee OA patients compared with placebo in a randomized, double-blind study.[28] Inhibition of 5-lipoxygenase by boswellic acids, especially acetyl-11-keto-β-boswellic acid (AKBA) is considered a major mechanism underlying the anti-inflammatory effects of *Boswellia*.[29-31] At preclinical level, oral and topical boswellic acids helped reduce cartilage loss and synovitis in a mouse model of OA.[32] *Boswellia serrata* topical formulation was shown to possess anti-inflammatory effects in rats with carrageenan-induced paw edema and was suggested as an alternative or combination therapy with NSAID in inflammatory diseases.[33] Topical capsaicin is recommended for relieving knee OA pain and is believed to exert its analgesic effects through downregulation of TRPV1 receptor activity on nociceptive sensory neurons and depletion of substance P.[34,36] *Pinus sylvestris* essential oil has been used in musculoskeletal complaints as per its commission E monograph.[37]

While the findings are promising, the relatively short duration (28 days) of the study and the lack of objective imaging or biochemical markers of inflammation (e.g., MRI findings, CRP levels, or synovial fluid biomarkers) can be considered as limitations of the study. Despite these limitations, the consistent efficacy across multiple outcome measures, combined with the excellent safety profile, supports the applicability of the findings to broader populations with mild-to-moderate knee OA. The formulation may offer a valuable adjunct or alternative to oral NSAIDs, particularly for patients who are contraindicated for systemic therapy or seek natural, well-tolerated topical options.

CONCLUSION

Overall, the results suggest that the topical pain relief cream formulation can contribute meaningfully to symptom relief, functional improvement, and quality of life in patients with knee OA when used as part of a comprehensive management strategy. Further studies involving extended treatment duration, mechanistic biomarkers, and comparison with standard topical NSAIDs could strengthen the evidence for its incorporation into routine OA care.

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