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Efficacy and safety of 6% cannabis extract pain relief gel in musculoskeletal and joint pain: A randomized open-label comparative study

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Abstract
Background: One of the most prevalent causes of pain, limited mobility, and a lower quality of life in adults is musculoskeletal and joint pain problems topical analgesics are participants first choice, as onset of action is quick and safe even when applied multiple times.
Methods: Thirty participants with acute or chronic musculoskeletal and joint pain disorders were randomized in an open-label, comparative clinical study design and were assigned to two groups where one group received test product which contained 6 % cannabis extract and other group received standard comparator gel. The onset of pain relief, complete pain relief was observed for 120 minutes post application, Visual Analog Scale (VAS) and Numerical Pain Rating Scale were used to measure the intensity of pain at rest and during movement. The Short Form 12 (SF 12) questionnaire was used to assess quality of life. Subject safety was assessed by pre and post systemic lab parameters in addition to adverse event monitoring.
Result: Pain Relief Gel with 6% Cannabis Extract demonstrated onset of pain relief, cooling/tingling/burning sensation and complete relief of pain at 2.67 ±1.49 minutes, 48.67±10.93 seconds and 66.07±36.05 minutes respectively, comparable to the standard comparator gel. Duration of action in Pain Relief Gel with 6% Cannabis Extract was 7.6±6.9 hours. Pain intensity measured at different timepoints related questioners were statistically significant in both the groups.
Conclusion: Pain Relief Gel with 6% Cannabis Extract reduced musculoskeletal and joint pain and improved quality of life in a safe and effective manner. Its therapeutic relevance as a topical analgesic alternative was supported by its effectiveness, which was equivalent to that of standard comparator gel.

Keywords: Cannabis extract, musculoskeletal pain, joint pain, visual analog scale

Introduction

Musculoskeletal and joint pain disorders are among the leading causes of physical discomfort, functional impairment, and diminished quality of life in adults. These conditions impose a significant global health burden, contributing substantially to long-term disability and accounting for a considerable proportion of orthopaedic outpatient visits worldwide. In addition to impairing mobility and daily functioning, they place considerable strain on healthcare systems and socioeconomic resources [1].

Effective management of these conditions aims to reduce pain and improve mobility, thereby enable individuals to perform their daily activities. Although non-steroidal anti-inflammatory drugs (NSAIDs) and oral analgesics are commonly prescribed, their long-term use is often limited by systemic adverse effects. In contrast, topical analgesic formulations have gained widespread acceptance due to their localized action, rapid onset of pain relief, improved patient compliance, and reduced systemic exposure [2].

Accurate and consistent assessment of pain intensity is essential in clinical studies to evaluate treatment efficacy. The Visual Analog Scale (VAS) is a validated, sensitive, and widely utilized instrument for measuring pain intensity in orthopaedic and musculoskeletal research [3]. Beyond pain reduction, improvement in overall health status and quality of life is a critical outcome in patients with chronic pain disorders. The Short Form-12 (SF-12) Health Survey, a well-validated tool, is commonly used to assess both physical and mental health domains [4].

The investigational product, Pain Relief Gel containing 6% cannabis extract, was developed for the management of joint and musculoskeletal pain. In response to the growing demand for safe and effective topical therapies, the present randomized, open-label, comparative clinical study was designed to evaluate the safety and efficacy of this formulation in adults with musculoskeletal and joint pain disorders, using validated measures of pain intensity and quality of life.

Materials and Methods

Study Design

The study was designed as randomized, open-label, comparative clinical study to assess the safety and efficacy of Pain Relief Gel with 6% Cannabis Extract in musculoskeletal and joint pain in adults for a period of 2 weeks.

Ethical Approval and Trial Registration

The study protocol was approved by the Ethics Committee, Ethique De La Nature Association (registration no ECR/376/Indt/PY/2023) for Thirumalai Medical Centre, Pondicherry and Oxymed Ethics Committee (registration no

ECR/1861/Inst/TN/2023) for Oxymed Hospital Chennai. The trial was registered prospectively in the Clinical Trials Registry of India (CTRI) on August 22, 2024, CTRI/2024/08/072903.

The study was carried out in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation – Good Clinical Practice (ICH-GCP) guidelines

Study Procedure

Adult participants with clinically confirmed acute or chronic musculoskeletal and joint pain and above eighteen years were screened for eligibility. Prior to enrollment, each subject gave written informed consent. 30 participants were enrolled in two groups

Participants with the below listed criteria were not enrolled in the study: history of hypersensitivity to topical analgesic formulations; skin infections; open wounds; dermatological conditions at the application site; use of corticosteroids; anti-inflammatory drugs; systemic analgesics within 48 hours before enrollment; pregnancy or lactation; and any serious medical condition that the investigator determines could affect study results.

30 participants were randomized into two groups, 15 in each.

- **Group 1- Test:** Participants (n=15) received Pain Relief Gel 6% Cannabis Extract, thrice daily topically for two weeks as directed by the investigator.

- **Group 2- Comparator:** Participants (n=15) received standard comparator gel, thrice daily topically for two weeks as directed by the investigator.

Randomization and Treatment Allocation

1:1 randomisation was used to place eligible individuals in either the test group (Pain Relief Gel 6% Cannabis Extract) or the comparator group (standard comparator gel).

Test or comparator products were administered topically to the afflicted region three times a day for 2 weeks. The participants were instructed to apply enough gel and massage gently until it was completely absorbed. During the trial period, no other topical or systemic analgesic medications were required for the participants.

Study Endpoint

Pain onset, onset of cooling/warmth/tingling/burning sensation and complete relief were assessed until 120 minutes post application of either test or comparator products. Pain intensity was measured used VAS scale. Reduction in pain score at rest and during movement was assessed using numeric pain rating scale. Inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were assessed at baseline and week 2.

The Short Form-12 (SF-12) questionnaire was used to measure physical and mental quality of life.

Statistical Analysis

Descriptive statistics were given for baseline characteristics like age, gender, any adverse events and tolerability profiles. The mean ± standard deviation was used to express continuous variables. Paired t tests were used for within-group comparisons, and the Mann Whitney test was used for between-group comparisons. P-values less than 0.05 were regarded as statistically significant. SPSS software was used for statistical analysis.

Result

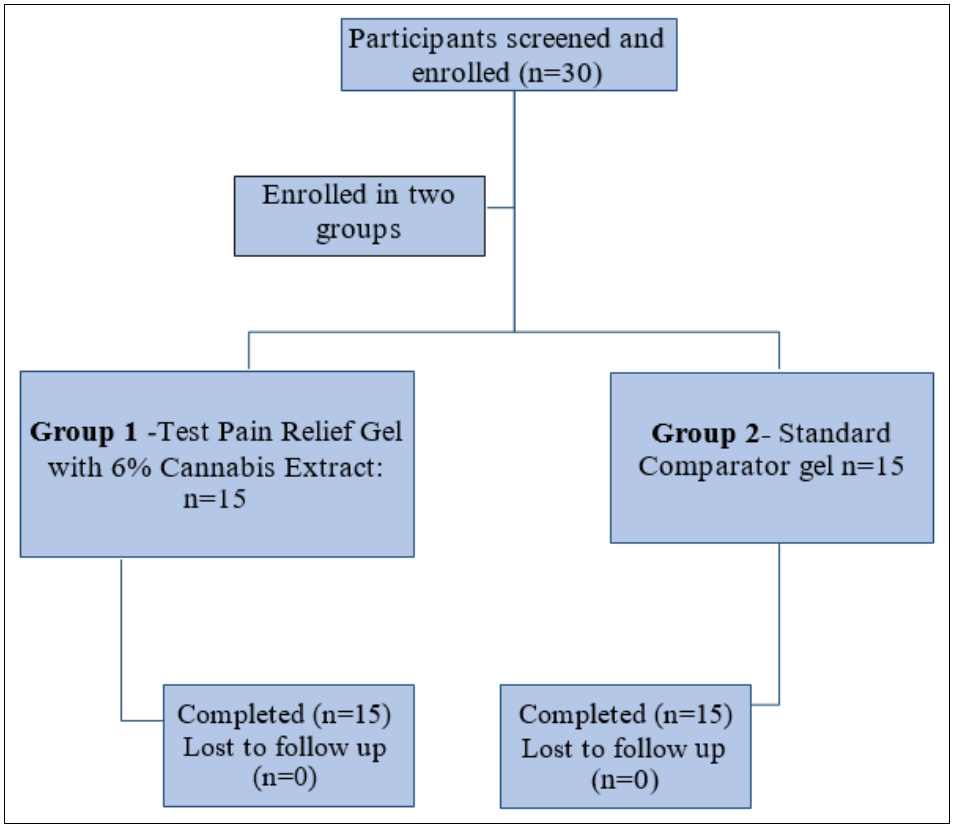

Fig 1: Participants Flowchart

Demographic Details

73% of male and 27% of female participants were randomised in the test group. Standard comparator gel 60% male and 40% female were enrolled in the comparator group, the gender distribution being similar between the two groups.

In the test group, 40% of participants were within healthy weight, 27% were obese, 20% were overweight, and 13% were underweight. In the Standard comparator gel group, 27% of participants were overweight, 20% were obese, and 7% were underweight, with 46% of participants falling into the healthy weight range as per the BMI.

Participants aged between 18-45 years were enrolled in both the groups.

Time to achieve pain relief

Showed a slightly faster onset of action (63.08 ± 18.319 seconds) compared to comparator (71.25 ± 20.24 seconds). Standard comparator gel Test group demonstrated complete pain relief at 13.69 ± 1.377 hours and the comparator group showed complete pain relief at Standard comparator gel13.92 ± 0.9 hours. Duration of action of the test product lasted for 3.08± 1.03 hours in test group, in the comparator it was found to be 2.92± 0.99 hours (Refer Table 1).

Table 1: Assessment of pain relief at various time points

Variables	Test (n=15)	Standard comparator gel (n=15)	p-value
	Mean ± SD	Mean ± SD	
Time to onset of pain relief (Sec)	63.08 ± 18.319	71.25 ± 20.24	0.3
Time to achieve complete pain relief (hr)	13.69± 1.377	13.92± 0.9	0.623
Duration of action (hr)	3.08± 1.038	2.92± 0.996	0.698

Reduction in Pain Scores

At rest and during movement, pain reduction was gradual and comparable over time in both the groups. Within-group analysis demonstrated significant reductions in pain scores over time for both groups.

Pain intensity measured using VAS Scale

VAS Score showed a statistically significant reduction in Joint/ musculo skeletal pain intensity in both the groups at week 2 compared to their baseline values (Table 2).

Between the two groups, the decreases were similar. This result is consistent with research showing that topical formulations containing menthol, diclofenac, or comparable drugs are useful in treating joint pain, particularly in disorders such as osteoarthritis [8]. The decrease in pain from the beginning to the end of therapy supports research showing that VAS values are accurate and sensitive indicators of treatment effectiveness [9].

Table 2: Joint/ Musculo skeletal pain intensity measured by VAS Scale

Study Visits	Test (n=15)	Comparator (n=15)
	Mean ± SD	Mean ± SD
Baseline	53.08± 9.473	51.67± 8.348
Week 2	30.38± 11.983	29.17± 11.645
P-value	0.0001	0.0001

Inflammatory Markers

Both groups demonstrated a statistically significant reduction in ESR levels at Week 2 compared to their baseline values. However, the between-group comparison did not demonstrate a statistically significant difference. CRP levels did not demonstrate statistically significant changes in either the within-group or between-group analyses (Table 3).

Table 3: Inflammatory Markers

Variables	Study Visit	Test	Comparator	p-value
		Mean ± SD	Mean ± SD	
ESR	Baseline	33.92± 13.481	35.5± 12.421	0.764
	Week 2	27.92± 13.357	28.5± 6.829	0.894
p value		0.003	0.029	-
CRP	Baseline	8.062± 3.2756	9.625± 4.1205	0.303
	Week 2	9.746± 8.5911	8.15± 3.5674	0.556
p value		0.483	0.528	-

Participant Overall Satisfaction for Pain Relief

In both groups, participant satisfaction levels increased from Baseline to the end of the study. Statistically significant improvement was observed within both the groups at week 2 compared to their baseline values in a 7-point likert scale.

User Perception on a 5- Point Likert Satisfaction Scale

Stickiness, greasiness, ease of application and ease of spreading was evaluated on week 2 using 5 point likert scale where lowest score means strongly disagree and the highest score denotes strongly agree. Ease of application in the test group was 3.77± 0.43, in the comparator it was 3.58± 0.51. Stickiness was found to be 2.92± 0.76 in the test and 3± 0.73 in the comparator. Greasiness in the test group was 2.92± 0.86, in the comparator it was 3.08± 0.51. ease of spreading remained 4 in both the groups (Table 4).

Table 4: User perception on a 5- point likert satisfaction scale

Variables	Test (n=15) (Mean ± SD)	Comparator (n=15) (Mean ± SD)	p- value comparison between groups
Ease of application	3.77± 0.439	3.58± 0.515	0.34
Stickiness	2.92± 0.76	3± 0.739	0.8
Greasiness	2.92± 0.862	3.08± 0.515	0.58
Ease of spreading	4± 0.707	4± 0.426	0.99

Quality of Life Assessment

SF-12 questionnaire was used to assess quality of life at baseline and at week 2. Both the Standard comparator gel test and comparator exhibited significant improvements across many domains.

General Health

Following 2 weeks intervention, participants in both the treatment groups reported a significant improvement in the assessed overall health. The percentage of individuals in the test group who rated their health as "Excellent" was 33.33%,

rated as "Very good" was 66.67%. In the comparator group 3.33% of participants reported their health as “Excellent” and 96.67% of participants reported as "Very good". Overall, the opinion of general health was improved by both treatments.

Physical Activity Limitations

In both the groups, at week 2 80% participants reported that they were limited a little to do moderate activities and 20 % of participants reported that they were not limited at all. Both groups demonstrated improvements in climbing stairs at week 2. 30% participants in the test group and 20 % in the comparator group demonstrated that they were not limited to climb several flights of stairs.

Emotional Well-being

Both groups demonstrated significant improvements in emotional health at week 2, 3.33 % of participants felt calm and peaceful “all of the time”. 96.67 % of participants felt it “most of the time”. 30% of participants felt downhearted and blue “A little of the time” at week 2.

Pain Interference with Work

At week 2, just "a little bit" of pain interference with normal work was reported by 96.67% of participants in both the groups, and "not at all" by 3.33%.

Social Activities

At week 2, 53.33% of participants reported Physical health or emotional problems interfered with the social activities "none of the time" and 43.33% reported interference "a little of the time." Standard comparator gel in both the groups.

Adverse Events and Safety Outcomes

Throughout the study, safety and tolerability were monitored by clinical monitoring and participant reporting. No adverse events were reported in either the test or Standard comparator gel groups during the 2 weeks treatment period. Throughout the study duration, no rescue medicine was required by the participants. Overall, the both topical formulations showed acceptable tolerability and a positive safety profile.

Discussion

Over the 2 weeks treatment period, this randomized, open-label comparative clinical trial showed that both Pain Relief Gel with 6% Cannabis Extract and Standard comparator gel achieved significant improvements in musculoskeletal and joint pain. Visual Analog Scale (VAS) scores, participant satisfaction ratings, SF-12 quality of life, and pain intensity at rest and during movement showed significant within-group changes. These results are in line with topical analgesic’s well-established function as useful choices for the treatment of localized musculoskeletal pain [11, 12].

The test product demonstrated a slightly faster onset of action compared to the comparator, indicating quicker initiation of pain relief following topical application. Rapid onset is an important attribute of topical analgesics as it helps provide prompt relief from localized joint and musculoskeletal pain. Both groups achieved complete pain relief at a comparable time point, suggesting similar overall effectiveness between the formulations. The duration of action lasted slightly longer in the test group compared to the comparator, indicating that the test product may provide marginally prolonged analgesic effects.

The therapeutic usefulness of topical analgesic formulations is supported by the observed reduction in joint and musculoskeletal pain VAS levels in both groups ($p = 0.0001$ across groups). In both acute and chronic pain investigations, VAS is universally acknowledged as a sensitive and trustworthy tool for identifying treatment-related changes in pain intensity [13].

Given the availability of topical analgesic and counter-irritant ingredients including menthol, camphor, and similar compounds, the quick start of pain alleviation and cooling feeling seen with both gels is pharmacologically reasonable. These substances provide quick but localized analgesic effects by activating transient receptor potential (TRP) channels, altering thermosensory pathways, and desensitizing peripheral nociceptor fibers [14, 15]. In comparison to systemic medication, previous clinical and mechanistic investigations have demonstrated that topical and menthol-based NSAID formulations can offer significant short-term relief for musculoskeletal and osteoarthritic pain disorders with positive safety profiles [11, 12].

The sensory attributes of the formulations, including stickiness, greasiness, ease of application, and ease of spreading, were evaluated using a 5-point Likert scale at Week 2. Both the test and comparator formulations demonstrated comparable user acceptability across these parameters. Ease of application and ease of spreading were rated favorably in both groups, indicating that the formulations were convenient to apply and spread effectively over the affected area. Stickiness and greasiness scores were also similar between the groups, suggesting comparable tactile characteristics following application. Overall, the findings indicated good user acceptability and comparable sensory properties for both formulations. Adherence to topical therapy is known to be significantly influenced by cosmetic acceptability and formulation aesthetics, especially in cases of chronic or recurring musculoskeletal disorders [16]. Both groups demonstrated a statistically significant reduction in ESR levels at Week 2 compared to baseline, suggesting improvement in the inflammatory status associated with musculoskeletal pain. However, the between-group comparison did not demonstrate a statistically significant difference, indicating comparable anti-inflammatory effects between the test and comparator formulations. ESR is widely used as an indirect marker of systemic inflammation and may decrease with effective therapeutic interventions targeting musculoskeletal conditions.

Both the groups showed significant improvements in the physical, emotional, and social aspects of quality of life as measured by the SF-12 questionnaire. Physical functioning, pain interference, mental well-being, social involvement, and general health perception all showed notable improvements. A popular and validated generic health status tool that is responsive to clinical change in populations with pain and musculoskeletal disorders is the SF-12 [17]. The QoL gains shown in this study are in line with other research demonstrating that quantifiable functional and psychological advantages result from good topical pain management [11, 12, 17].

Conclusion

The results of this randomized, open-label comparative clinical trial demonstrated that both the Pain Relief Gel with 6% Cannabis Extract and the standard comparator gel were effective in reducing musculoskeletal and joint pain over the 2-week treatment period. Significant improvements were observed in pain intensity, participant satisfaction, and quality of life measures within both groups. The test formulation exhibited a slightly faster onset and marginally longer duration of action, while overall efficacy remained comparable between the two formulations.

Both products were well tolerated and showed good user acceptability in terms of sensory attributes such as ease of application, spreadability, stickiness, and greasiness. Improvements in inflammatory markers, particularly ESR, further supported the beneficial effects of topical therapy in managing musculoskeletal pain. Additionally, the observed improvements in SF-12 scores indicated a positive impact on participants' physical and mental wellbeing.

Overall, the findings suggest that the Pain Relief Gel with 6% Cannabis Extract represents a safe, well-accepted, and effective topical option for the management of localized musculoskeletal and joint pain, with efficacy comparable to the standard comparator gel.

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Conflicts of Interest: None

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