

Research Article

The Effect of Topical Palmitoylethanolamide (PlexoZome Levagen) on Relief of Post Exercise Knee Joint Pain – A Randomised Double-Blind Controlled Study

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Abstract

Joint pain is a common ailment that can arise from several different causes and may affect people of any age. It can negatively impact quality of life and represents a significant global health concern. Conventional pain-relieving medications provide relief for many, however, may be associated with adverse effects. Palmitoylethanolamide (PEA) is a naturally occurring fatty acid amide with known anti-inflammatory and analgesic effects. This study aimed to assess the effectiveness of a topical PEA (PlexoZome Levagen) spray on relieving knee joint pain post-exercise. This was a double-blind, placebo-controlled study on 86 adults who experienced post-exercise knee pain. Upon a knee pain rating of $\geq 3/10$ on the VAS pain scale, participants applied 3 sprays of their investigational product (PEA or placebo). Participants recorded their pain on the VAS every 15 minutes for a maximum of 2 hours or until their pain subsided. If still experiencing pain, participants reapplied their investigational product at the 30-, 60- and 90- minute mark. A total of 214 pain episodes qualified for analysis, with the PEA group significantly resolving more pain events within 60 minutes of onset compared with the placebo. At 60 minutes, the PEA group significantly reduced pain from base-

line by 71% compared to a 43% reduction in the placebo group. No adverse effects were noted in either group. Topical application of PEA was found to be safe and effective in relieving knee pain post exercise and further studies investigating its analgesic effects are warranted.

Keywords: Exercise; Knee Joint Pain; Palmitoylethanolamide; PEA

Introduction

Palmitoylethanolamide (PEA) is known for its analgesic, anti-inflammatory, and immune-modulating effects [1]. PEA shows promise in treating conditions such as hypersensitivity, arthritis, inflammatory bowel disease, neuropathic pain, and neurodegenerative diseases (Alzheimer's, Parkinson's, and multiple sclerosis) [1,2]. PEA's mechanism involves actions on receptors such as PPARs and TRPV1 [1], inhibition of pro-inflammatory molecules [3], and potentially boosting the endocannabinoid system [1,4]. Despite PEA's potential health benefits, clinical studies on its effectiveness and safety, particularly for joint pain, remain limited and require further research.

Joint pain is a common clinical issue with various causes, often linked to inflammatory mediators that activate sensory nerves and cause pain [1]. Knee pain alone accounts for around 5% of adult primary care visits, with common causes including osteoarthritis, patellofemoral pain syndrome, and meniscal tears [5]. Effective treatment depends on the underlying cause. Exercise therapy can reduce pain perception and improve mental health, but it may also induce pain, leading some individuals to avoid exercise-based rehabilitation [6].

Oral pain-relieving medications, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), are commonly used to manage knee pain [7]. However, there are notable risks associated with their long-term use [8]. Topical analgesic preparations are widely used for both acute and chronic joint pain, with evidence supporting their use in treating certain musculoskeletal conditions, such as sprains and strains [9,10]. A recent systematic review reported that topical NSAIDs are as effective as oral NSAIDs in reducing pain and improving physical function in patients with osteoarthritis, and that they may offer a safer alternative to oral medications [11].

The use of complementary medicines is becoming increasingly prevalent as a treatment option for managing joint pain and inflammation [12]. PEA is an endogenous saturated fatty acid derivative synthesized from palmitic acid within the lipid bilayer and is believed to be produced as a protective response to cellular injury. PEA has demonstrated numerous disease-modifying effects and may provide therapeutic benefits for a wide range of conditions [13]. Numerous studies have supported the effectiveness of PEA in the treatment of pain [14].

A recent systematic review and meta-analysis, which included 11 studies and a total sample of 774 patients, found that PEA significantly reduced pain and improved quality of life in chronic pain sufferers,

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with no major adverse effects reported [14]. In one clinical study on knee pain related to osteoarthritis, oral administration of 300mg or 600mg of PEA resulted in significant reductions in pain and stiffness after 8 weeks of use [15].

To date, no studies have examined the effectiveness of externally applied PEA for knee pain. The aim of this study was to assess the effectiveness of a topical PEA spray (PlexoZome® Levagen®) on relieving post-exercise knee joint pain compared to a placebo.

Methodology

This study was conducted as a randomised, double-blind, placebo-controlled study, investigating the effect of the investigational use of a topical PEA on post exercise knee pain. Both the PEA (PlexoZome Levagen - a liposomal form of PEA), and the placebo were produced by Pharmako Biotechnologies Pty Ltd (Sydney, Australia) and encapsulated in their TGA approved facility according to good manufacturing practice condition. The study was conducted as a remote study (i.e., no face-to-face contact) between April and June 2024. Participants were recruited from across Australia and those who were over 20 years of age, generally healthy, undertaking regular exercise and experiencing post exercise knee pain of a minimum rating of 3 out of 10 at least twice in the previous 4 weeks, were included. Participants needed to agree not to change their current diet or exercise frequency or intensity for the duration of the study. Exclusion criteria included: any unstable or serious illness (e.g. diabetes, thyroid gland dysfunction, mood disorders, neurological disorders, kidney disease, liver disease or heart condition), malignancy (excluding basal cell carcinoma) or treatment for malignancy within the previous 2 years, anticoagulation therapy, tobacco use, alcohol or drug abuse (prescription or illegal substances), allergy to any ingredients in the active or placebo formula, pregnant or lactating women, and any condition which the investigator believed made the participant unsuitable for inclusion. Diclofenac tablets, capsules or topical gel or spray and common pain relief analgesics such as paracetamol and ibuprofen were not permitted to be taken within the 2 hours that pain scores were recorded.

Eligible participants provided their written informed consent prior to being randomly allocated to one of two study groups (active or placebo) in a 1:1 ratio. Randomisation was conducted by an independent person using randomisation allocation software (www.sealedenvelope.com), with both the participants and investigators blinded to the product allocation.

Participants in the treatment group received a topical PEA spray (PlexoZome® Levagen®) with a dose of 1.8 mg of PEA per spray. The placebo group received an unmedicated aqueous based spray, identical in appearance and consistency to the PEA spray. The treatment and placebo products were packaged in identical opaque containers and labelled in the same manner except for the product number, which was obtained from the randomisation code.

Following enrolment, self-reported height and weight measures were obtained, and BMI calculated for demographics purposes. Participants were then sent their trial product and asked to monitor their post-exercise knee pain, which was defined as knee pain experienced within 24 hours of exercise cessation. Participants were able to record up to five knee pain treatment episodes, over a maximum four-week period. Only one knee pain treatment episode could be recorded within a 24-hour period. Participation in the study was concluded once five episodes or the four-week study period was completed.

Participants initiated a knee pain recording episode when they experienced post-exercise knee pain that was rated ≥ 3 on a Visual Analogue Scale (VAS). The VAS Pain Scale is a scale of 0 -10, where 0 was defined as 'no pain' and 10 defined as 'pain as bad as it could possibly be'. Pain scores were registered online via a participant specific secure website login provided at enrolment.

Upon the onset of knee pain, participants completed the online VAS Pain Scale before applying 3 full pumps of spray onto the affected knee area, without rubbing the preparation into the skin. Following application, participants completed the online VAS Pain Scale rating every 15 minutes for up to 2 hours, or until their knee pain was resolved (pain score of 0/10).

If knee-pain persisted, participants were asked to apply an additional 3 full pumps of spray onto the affected area 30-, 60- and 90-minutes post onset. Rescue analgesic medication was not permitted during the two hours of the knee pain treatment. If rescue medication was used, the participants data for that event was excluded from analysis. Participants were monitored for dosing compliance, adverse events and rescue medication use through regular check-ins conducted by phone, text and email.

The primary outcome of the study was the difference between groups for change in knee pain as measured by the VAS Pain Scale. Secondary outcome measures included time to pain relief via the VAS Pain Scale, number of resolutions between groups, safety via adverse event monitoring and rescue medication use via self-report.

The sample size was calculated using G*power (v3.0.10), accounting for an α error probability of 0.05 and powered to 0.95 for a 25% difference in VAS reduction between groups. The resulting effect size calculated from values obtained from published studies, was $d = 0.8$. Therefore, group sizes of at least 35 events per group were required. Allowing for dropouts, group sizes of approximately 40 participants were chosen to allow an average of 1 event per participant over 4-weeks.

Statistical analyses were performed using IBM SPSS Statistics (version 25.0) for Windows (IBM, Chicago, IL, USA). Differences between groups were assessed using independent t-tests and covariates accounted for with an ANCOVA. Differences between the number of episodes per group and rescue medication use was assessed using Chi Squared tests and changes in pain was analysed using Kruskal-Wallis tests adjusted for pair-wise multiple comparisons with Bonferroni corrections. Statistical significance was set at $p < 0.05$. Subgroup analysis was conducted on initial severity of pain where the starting pain was either mild-moderate (a score of 3-5 on the VAS) or severe (a score >5 on the VAS). Any single missing data point was analysed as intention-to-treat (ITT).

This trial was conducted in compliance with the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Therapeutic Goods Administration (TGA) Note for Guidance on Good Clinical Practice, and in accordance with ethical approval from Bellberry Limited, an NHMRC accredited Human Research and Ethics Committee. The study was registered on ClinicalTrials.gov (NCT06351917). Participation was voluntary and all participants provided written informed consent prior to starting.

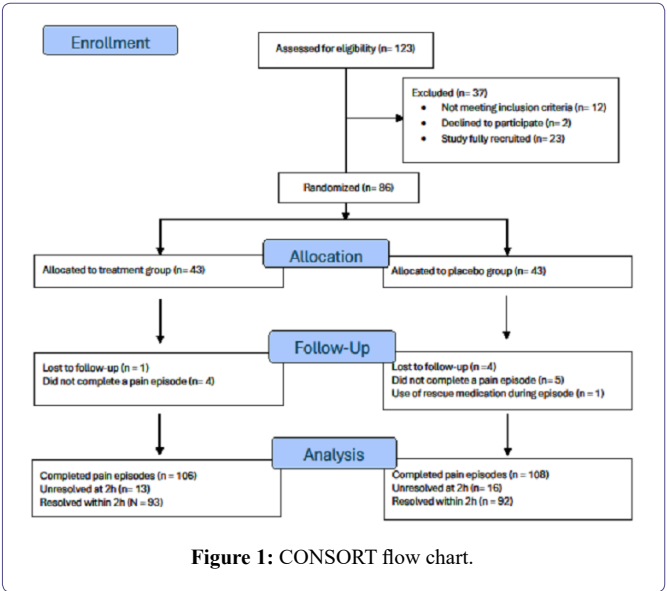
Results

86 participants were enrolled into this study, with 81 considered to have completed the trial and five people lost to follow-up with no

reason given. There was no significant difference in demographics between groups (Table 1). Of the five participants lost to follow-up, one registered a pain event and was included in the analysis. Of the 86 participants enrolled, 77 participants recorded at least one pain episode, with a total of 230 pain episodes recorded. Of the pain episodes recorded, 2 (placebo group) events from a single participant were excluded due to rescue medication use for menstrual pain and a further 14 were excluded from analysis due to more than 3 consecutive data points missing or incorrect entry by the participant. 214 completed knee pain events were therefore used in the final analysis. Of the 214 pain events included in final analysis, 185 were resolved within the 2-hours of recording (Figure 1).

	Active (n = 43)	Placebo (n = 43)
Age (mean ± SD [range])	43.1 ± 12.1 [22-64]	46.0 ± 14.9 [20-70]
Gender (M/F)	17 / 26	16 / 27
Weight (kg) (mean ± SD [range])	75.3 ± 15.7 [48-103]	75.2 ± 17.4 [50-115]
Height (meters) (mean ± SD [range])	1.71 ± 0.08 [1.56-1.86]	1.68 ± 0.09 [1.5-1.85]
BMI (mean ± SD [range])	25.6 ± 4.57 [18.82-37.89]	26.4 ± 5.29 [17.87-44.37]
At least one pain episode recorded (n)	40	37
Total pain events (n)	106	108
Resolved pain events (n)	93	92

Table 1: Participant Demographics.



Of the 214 events, there was no significant difference between groups for the total number of events that were unresolved after 2-hours of treatment (n=13 in the active and n=16 in the placebo group; Figure 2). The active group had significantly more events resolved at 60 and 75 minutes compared to the placebo group (p<0.05; Figure 2). The active group had a significantly lower pain score at 60 minutes compared to the placebo group (Table 2). Pain reduction at 60 minutes equated to a 55% and 36% reduction in pain relative to baseline for the active and placebo group respectively (p<0.05; Table 2).

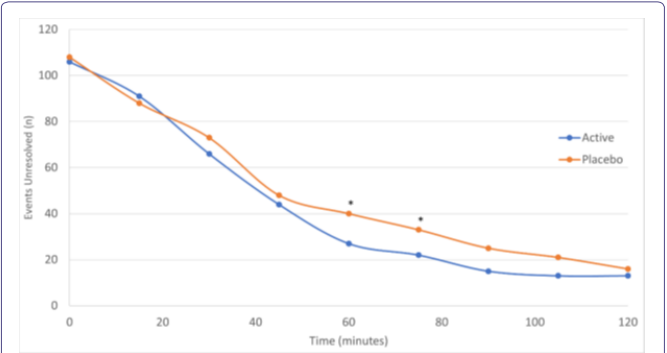


Figure 2: Number of unresolved pain events over 2 hours.

	Pain onset	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Active	4.94 ± 1.50	3.58 ± 2.13	2.84 ± 2.23	2.33 ± 2.21	2.20 ± 2.28	2.85 ± 2.27	2.55 ± 2.43	3.13 ± 2.53	3.69 ± 2.43
Placebo	4.75 ± 1.52	3.27 ± 2.27	3.07 ± 2.15	2.44 ± 2.25	3.02 ± 1.97	2.70 ± 1.82	2.55 ± 1.97	2.68 ± 1.69	2.33 ± 1.73
p-value	0.18	0.16	0.24	0.39	0.04*	0.39	0.50	0.28	0.05

Table 2: Pain rating for all events (VAS scores). Once an event was resolved, it was not included in the following time point calculation.

*Significant difference between active and placebo groups.

When unresolved events were excluded, results were equivalent to that of all the data. Of the 185 resolved events, the average time to resolution was 45.1 minutes in the active group, and 50.2 minutes in the placebo group (Table 3). When time to resolution was considered, significantly more resolutions occurred in the PEA treatment group within the first 60 and 75 minutes (p < 0.05; Table 3 & Figure 2) compared to the placebo.

	Active	Placebo
No. of unresolved pain episodes at 2 h	13	16
No. of resolved episodes (N= 93)	(N= 93)	(N= 92)
Pain resolved by 15 minutes [n (%)]	15 (16.1)	20 (21.7)
Pain resolved by 30 minutes [n (%)]	40 (43.0)	35 (38.0)
Pain resolved by 45 minutes [n (%)]	62 (66.7)	60 (66.7)
Pain resolved by 60 minutes [n (%)]	79 (84.9) *	67 (72.8)
Pain resolved by 75 minutes [n (%)]	84 (90.3) *	75 (81.5)
Pain resolved by 90 minutes [n (%)]	91 (97.8)	83 (90.2)
Pain resolved by 105 minutes [n (%)]	93 (100)	87 (94.5)
Pain resolved by 120 minutes [n (%)]	93 (100)	92 (100)
Time to resolution (minutes; mean ± SD)	45.1 ± 22.91	50.2 ± 30.52

Table 3: Pain resolution time for events that were resolved.

*Significant difference between active and placebo groups.

There was no significant difference between groups for the initial reported pain score (Active 4.89 ± 1.47 Vs. Placebo 4.63 ± 1.46). At 60 minutes post treatment, there was a significant reduction (p < 0.01) in pain from baseline in the active group (-3.48 ± 1.79) compared to the placebo (-1.98 ± 2.11; Table 4). A further significance between

groups was observed at 105 minutes ($p = 0.01$). However, only 11 pain events (2 in the active and 9 in the placebo group) remained unresolved at this point (Table 4 & Figure 2).

	Pain onset	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Active	4.89 ± 1.47	3.39 ± 2.11	2.51 ± 2.10	1.88 ± 1.94	1.41 ± 1.79	1.78 ± 1.74	0.66 ± 1.25	0 ± 0	N/A
Placebo	4.63 ± 1.46	2.96 ± 2.19	2.65 ± 2.02	1.96 ± 2.22	2.66 ± 2.12	2.17 ± 1.97	1.71 ± 2.19	1.56 ± 1.71	0.00 ± 0.00
p-value	0.10	0.08	0.34	0.42	0.008*	0.28	0.08	0.02*	N/A

Table 4: Pain rating for resolved events (VAS). Once an event was resolved, it was not included in the following time point calculation.
*Significant difference between active and placebo groups.

Analysis of resolved pain events for severity, showed those events rated as mild-moderate (3-5 on the VAS) showed no difference in resolution time. However, equivalent to the full data set, pain at 60-minutes was lower in the active group (1.57 ± 1.56) compared to the placebo group (2.26 ± 1.17 ; $p < 0.05$).

For events with an initial pain score of severe (>5 on the VAS), the average time to resolution was significantly quicker in the active group compared to the placebo ($p < 0.05$; Table 5). Pain at 45-minutes was lower in the active group (2.94 ± 2.63) compared to the placebo group (4.17 ± 2.37 ; $p < 0.05$). No adverse effects were noted in either group.

	Initial Pain	Average Resolution time (minutes)
Pain 3-5 (mild-moderate)		
Active (N= 69)	3.99 ± 0.81	48.70 ± 33.34
Placebo (N = 82)	4.02 ± 0.75	52.50 ± 35.16
Pain 6-9 (moderate-severe)		
Active (N= 38)	6.63 ± 0.81	65.92 ± 28.70*
Placebo (N = 26)	7.04 ± 0.98	85.96 ± 33.17

Table 5: Subgroup analysis based on severity at onset.
*Significant difference between groups $p < 0.05$.

Discussion

This study assessing the effectiveness of a topical PEA spray (PlexoZome® Levagen®) on relieving knee joint pain post-exercise compared to a placebo, demonstrated several key findings. Notably, pain resolution times were faster in the PEA group, and the pain reduction was more pronounced, especially at the 60-minute mark. These results provide valuable insights into the effectiveness of PEA and contribute to a growing body of literature on pain management.

The study enrolled 86 participants, with 81 completing the trial. Demographic factors such as age, weight, height, and body mass index (BMI) were well-matched between the active and placebo groups, suggesting that any differences in outcomes are likely attributable to the treatment rather than confounding factors. Participant retention was high, with only five lost to follow-up, indicating good adherence to the study protocol. The number of pain episodes recorded was also nearly identical between the groups, ensuring robust data for comparison.

One of the most important findings of this study was the difference in pain resolution between the two groups. Of the 214 pain events included in the analysis, the majority (185) were resolved within two hours of recording. Both the active and placebo groups had similar numbers of unresolved events at two hours. However, the active group demonstrated a faster pain resolution, with significantly more pain events resolving within 60 and 75 minutes compared to the placebo group.

This difference in resolution time is a crucial outcome. The active group resolved 84.9% of pain events by 60 minutes and 90.3% by 75 minutes, compared to 72.8% and 81.5% in the placebo group, respectively. The faster pain resolution in the active group is consistent with the primary hypothesis that the active treatment is more effective at managing knee pain. The significantly lower pain score in the active group at 60 minutes further supports this finding, with a 55% reduction in pain from baseline compared to a 36% reduction in the placebo group. This rapid reduction in pain is of practical importance for people seeking fast relief.

The subgroup analysis also provides interesting insights into the efficacy of PEA based on the severity of pain. For events with moderate-to-severe pain, the PEA group experienced a significantly faster resolution time compared to the placebo group (65.92 minutes vs. 85.96 minutes). This result suggests that PEA may be particularly effective for individuals experiencing more intense knee pain, which is critical to tailor treatments to patient needs.

The findings of this study are in keeping with those identified in an 8-week randomised controlled trial that compared the efficacy and safety of two different doses of oral PEA (300 mg or 600 mg day) to placebo on symptoms of knee osteoarthritis. The results showed statistically significant improvements in pain, stiffness and functionality in the PEA groups compared to placebo [15]. PEAs usefulness in relieving pain was further examined in a systematic review and meta-analysis which included 11 studies conducted on chronic pain. The study found that PEA reduced pain scores, and no major adverse effects were noted in any of the studies; this data suggests that PEA is an effective and well-tolerated treatment for pain [14].

When comparing these results to other studies on knee pain management, the findings align with research on non-steroidal anti-inflammatory drugs (NSAIDs), which are commonly used for pain relief. A systematic review on NSAIDs and opioid treatment for knee and hip osteoarthritis found that NSAID-treated patients reported significant improvements in pain. Oral NSAIDs were found to be the most effective for pain relief, while opioids were less effective for pain relief and carried significant risks for adverse events and dependency [16]. Topical NSAIDs also provide pain relief, albeit less so than oral NSAIDs, but with fewer side effects, making them a potentially safer long-term option [6]. Although generally safer, topical NSAIDs may still cause side effects [17].

Long term oral NSAIDs use may be detrimental compared to non-use. A study by Salis and Sainsbury (2024) [18] found individuals using NSAIDs long-term (over 4-to-5 years) had an increased likelihood of aggravated knee pain symptoms and were more likely to have total knee replacement, despite no difference in structural deterioration, compared to non-users. PEA may offer a more favourable safety profile for both short- and long-term use compared to NSAIDs.

Studies comparing the analgesic and anti-inflammatory effects of PEA to NSAIDs, are limited. One study compared the effect of an oral

PEA to an NSAID (Ibuprofen) for the relief of temporomandibular joint (TMJ) pain due to osteoarthritis or arthralgia in 24 participants over 14 days. The results showed that pain reduction was significantly greater in the PEA group, compared to the NSAID group, suggesting that PEA is effective in relieving TMJ pain [19]. A comparison of the safety and effectiveness of PEA and NSAIDs represents an avenue that needs further exploration.

Further comparison can be made with studies on topical analgesics. Bariguan et al. (2020) [20] studied the effects of a diclofenac patch (an NSAID) for knee osteoarthritis, finding pain relief occurred within the first hour of application, with significant reductions continuing over subsequent hours, similar to the time observed in the PEA group in the current study.

Topical analgesic medications like diclofenac are commonly used to treat acute and chronic pain. They are absorbed through the skin and exert their effects locally. Evidence supports the use of topical NSAIDs in treating acute musculoskeletal conditions [10] and are typically associated with lower rates of adverse effects compared to oral treatments. This is largely due to minimal systemic absorption, offering a preferred safety profile [21]. Furthermore, some oral treatments, like PEA, tend to have low bioavailability when taken orally due to their lipophilic nature [13]. Topical formulations of PEA may therefore offer an effective alternative treatment option to oral forms.

Another benefit of topical application is the ability to target the area in need of treatment. Oral treatments offer a systemic treatment modality, whereas topical application allows the treatment to be targeted to the site of pain [21]. This may offer greater efficacy in alleviating acute pain but would need to be confirmed by future studies.

Although the study produced promising results, there are several limitations to consider. The study was relatively small, with only 86 participants, which may limit the generalizability of the findings. Larger studies with more diverse populations are needed to confirm these results. Another limitation is that while the active treatment appeared effective in managing knee pain, future studies should examine its effectiveness in comparison to NSAIDs, which while effective, have well-documented adverse effects.

Further limitations that may be considered due to the study included participants with various underlying pathologies for their knee pain. While the two groups were similar at baseline with regards to age, gender and pain scores, it may be of value to focus the study on a particular knee pain pathology. Another limitation is that some participants experienced technological difficulties when recording the VAS scores and several participants did not strictly adhere to the required time points resulting in incomplete episodes. ITT was used to combat this; however, a number of episodes were excluded as more than 3 time points were missing. Another limitation is the short duration of the study. A small number of participants did not experience a knee pain episode within the four-week study period and so did not record any pain episodes. Also, it would be of value to investigate the long-term use of the PEA spray on both exercise-induced knee pain and other knee pain pathologies such as osteoarthritis.

Overall, this study adds to the growing body of research on both the effectiveness of PEA and knee pain management by demonstrating that PEA treatment provided faster and more significant pain relief compared to a placebo. Pain resolution occurred more quickly, particularly in cases of moderate-to-severe pain, and PEA treatment

consistently reduced pain scores more effectively than the placebo at key time points. These results suggest that PEA treatment could be a valuable option for individuals experiencing knee pain, offering rapid relief with potentially fewer side effects than traditional treatments such as NSAIDs. However, further research is needed to confirm these findings in larger populations and to evaluate the long-term efficacy of this treatment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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