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Research Article

Evaluation of the Analgesic Effect of a New Topical Composition based on *Cannabis sativa* Oil Enriched in Cannabidiol, Escin, Bromelain, Boswellia Extract, Glucosamine sulphate, Methylsulfonylmethane and Methylsalicylate

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ABSTRACT

Objective: The aim of this study is to evaluate the analgesic effect of the new lipogel formulation based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®), in patients with localized pain related to acute minor musculoskeletal conditions.

Methods: In this study 60 patients with pain due to one of the following conditions: tendinitis of the upper or lower limbs, low back pain, knee and ankle sprains/contusions, sport-related soft-tissue injury (sprains, strains and contusions) of upper or lower limbs, cervicalgia (neck pain), myalgias, arthrosis, carpal-tunnel syndrome, were included in the evaluation. Patients were allocated to treatment with the new lipogel formulation three times a day for 7 days and were evaluated at 5 timings: T0 (baseline), T1 (30 minutes after first application), T2 (1 day after first application), T3 (3 days after first application) and T4 (7 days after first application) by assigning a score in a 100-mm Visual Analogue Scale (VAS). The primary objective was to assess the analgesic effect by using the reduction of VAS score from T0 to T4. The secondary outcome was to obtain information on the safety of locally applied product.

Results: The results showed a statistically significant VAS score reduction versus baseline for each time point evaluated, with a mean reduction from 77.52 registered at T0 to 30.55 registered at T4 ($P<0.001$). The mean VAS score from T0 to T4 was reduced of about 47%. Regarding the secondary safety outcome, the gel application was well tolerated, and no adverse events were reported.

Conclusion: This study confirmed the analgesic effect of a new topical composition based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®), in patients with localized pain related to acute minor musculoskeletal conditions.

Keywords: Cannabidiol; Escin; Bromelain; Boswellia extract; Glucosamine sulphate; Methylsulfonylmethane; Methylsalicylate; Musculoskeletal conditions.

INTRODUCTION

Emerging scientific evidence is arising about the use of topically administered Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for numerous musculoskeletal conditions, both acute pathologies like sprains, strains, bruises and muscular contractures, and chronical conditions that can derive, for example, from osteoarthritis, chronic joint degeneration, or overuse injuries [1,2].

Increased use of topical drugs is mainly aimed to avoid the occurrence of adverse events related to systemic therapy with nonspecific oral NSAIDs such as GI irritation and ulceration, increased risk of bleeding (mainly gastrointestinal), kidney or liver disorders [2,3].

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Topical application enables to have a direct action on painful site, bypassing systemic absorption and thus obtaining a local pain-relieving and anti-inflammatory effect. This route of administration is suitable for superficial painful and inflammatory conditions affecting muscles, tendons and joints, otherwise is not useful for deep visceral pain and in case of open wounds [2,4].

The stratus corneum is the more external layer of epidermis that has barrier and protective functions. Active ingredients to be used in a topical formulation for exerting their action must penetrate the skin by crossing stratus corneum and, once arrived in the epidermis and dermis will show local action, without being absorbed systemically [2,5].

Along with topical use of NSAIDs, evidence is growing on the use of naturally derived compounds to be applied locally for pain-relieving and anti-inflammatory action in different patient settings [6,7]. For example, topical application of hemp oil extract from several parts of *Cannabis sativa* plant, showed important results in reduction pain and inflammation in different *in vivo* models and in humans. Hemp oil extract contains cannabinoids or phytocannabinoids derivatives, including cannabidiol, one of more studied active constituents of the plant, along with Delta (9)-TetraHydroCannabinol (Δ9-THC), the psychoactive compound. CBD is one of the main active ingredients of *Cannabis sativa* without psychotropic activity but with important therapeutic actions mediated by several and complex mechanisms involving different receptors and signaling pathways [8,9]. A lot of studies explored CBD topical activity, both in animal models, including a Croton oil mouse ear dermatitis [10], a mouse model of experimental autoimmune encephalomyelitis [11], a rat model of arthritis [12], and in humans, like patients with inflammatory skin disorders [9] and patients with peripheral neuropathy [13].

Topical application of other active ingredients of natural origin has been studied for different compounds like escin, isolated from horse chestnut (*Aesculus hippocastanum*), that showed efficacy in pain reduction in patients with acute impact injuries [14,15]. Escin in combination with *Boswellia serrata* extract and other herbal ingredients showed improvements in clinical symptoms of localized neck/shoulder pain [16]. Topical application of boswellic acids (isolated from *Boswellia serrata*) showed efficacy in the treatment of erythematous eczema and psoriasis [17] and demonstrated anti-inflammatory activity in acute and chronic models *in vivo* of inflammation [18]. Bromelain, which represent an extract of proteolytic enzymes obtained from the stem and fruit of the pineapple plant (*Ananas comosus*), showed to accelerating healing process in bruises, hematomas, and musculoskeletal injuries, furtherly, it is effective in wound debridement [19].

Topical formulation based on glucosamine sulfate and chondroitin sulfate showed efficacy in pain reduction in patients with osteoarthritis of the knee [20]. In addition, also local use of methyl salicylate in gel preparation showed a beneficial analgesic and local anti-inflammatory effect in patients with rheumatoid arthritis [21].

A new topical composition based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®) has been designed for local treatment of inflammatory and painful conditions affecting joints, muscles, tendons and/or ligaments. All active ingredients have been added into this composition in order to improve analgesic and anti-inflammatory efficacy, exploiting the synergism of action of single compounds. An *in vitro* permeability study conducted on four several formulations of above-mentioned active ingredients that differed for type of vehicle, allowed to establish the better formulation for final product [22].

The aim of this study is to evaluate the analgesic effect of the new lipogel formulation based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®), in patients with localized pain related to acute minor musculoskeletal conditions.

MATERIALS AND METHODS

A total of 60 outpatients of both sexes (32 males, 28 females), mean age 55.02 (± 14.2) years, with pain due to one of the following conditions: tendinitis of the upper or lower limbs, low back pain, knee and ankle sprains/contusions, sport-related soft-tissue injury (sprains, strains and contusions) of upper or lower limbs, cervicalgia (neck pain), myalgias, arthrosis, carpal-tunnel syndrome, were included in the evaluation. Details of musculoskeletal conditions are reported in Table 1.

Table 1: Baseline characteristic of enrolled patients.

Variable	Patients (N=60)
Male/female, N	32/28
Age (years), mean (± SD)	55.02 (14.2)
Tendinitis of the upper or lower limbs, N (%)	16 (26.7)
Low back pain, N (%)	10 (16.7)
Knee and ankle sprains/contusions, N (%)	9 (15)
Sport-related soft-tissue injury (sprains, strains and contusions) of upper or lower limbs, N (%)	8 (13.3)
Cervicalgia (neck pain), N (%)	6 (10)
Myalgias, N (%)	5 (8.3)
Arthrosis, N (%)	4 (6.7)
Carpal-Tunnel Syndrome, N (%)	2 (3.3)

Patients were allocated to treatment with the lipogel formulation based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®, AQMA Italia S.p.A.) three times a day for 7 days. Patients received instructions regarding the application of the lipogel composition that was applied on the painful part and massaged gently until absorption. Subjects were informed of the study procedures and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects.

Patients were evaluated at 5 timings: T0 (baseline), T1 (30 minutes after first application), T2 (1 day after first application), T3 (3 days after first application) and T4 (7 days after first application). All patients filled in an assessment questionnaire at each time point, registered at the same hour for every day of assessment, except for T1, assigning a score from 0 to 100 to perceived pain, using a 100-mm Visual Analogue Scale (VAS). Information regarding adverse events eventually reported was added as evaluation of safety. The questionnaire also provided a question about the benefit obtained from the treatment at day 7 (T4) and its entity, explained by following parameters: a) no benefit; b) real benefit; and c) great benefit.

The primary objective was to assess the analgesic effect of lipogel application on localized pain related to acute minor musculoskeletal conditions, by using the reduction of VAS score from T0 to T4. The secondary outcome was to obtain information on the safety of locally applied product.

Statistical analysis was performed using Paired T-test with Microsoft excel analysis program for Windows 11 Pro, by comparing all VAS scores registered in the study collected from T0 to T4. The differences were considered significant when $P<0.05$.

RESULTS

This study was conducted to evaluate the analgesic effect of a new topical composition based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®), in 60 consecutive outpatients with localized pain related to acute minor musculoskeletal conditions, such as tendinitis of the upper or lower limbs, low back pain, knee and ankle sprains/contusions, sport-related soft-tissue injury (sprains, strains and contusions) of upper or lower limbs, cervicalgia (neck pain), myalgias, arthrosis, carpal-tunnel syndrome. This effect was evaluated trough collection of VAS scores at several time points (T0-T4) after starting treatment and mean results are reported in Table 2. The results showed a statistically significant VAS score reduction versus baseline for each time point evaluated, with a mean reduction from 77.52 registered at T0 to 30.55 registered at T4 ($P<0.001$). The mean VAS score from T0 to T4 was reduced of about 47% (Figure 1).

Table 2: Mean VAS scores over treatment period.

Timepoint*	T0	T1	T2	T3	T4	P value
Mean VAS score	77.52	70.5	63.07	48.62	30.55	<0.001
Standard deviation (± SD)	7.98	11.68	10.14	13.19	18.67	-

*T0: baseline; T1: 30 minutes after first application; T2: 1 day after first application; T3: 3 days after first application; T4: 7 days after first application. Means ± SD (N=60). P<0.001 for all time points versus baseline.

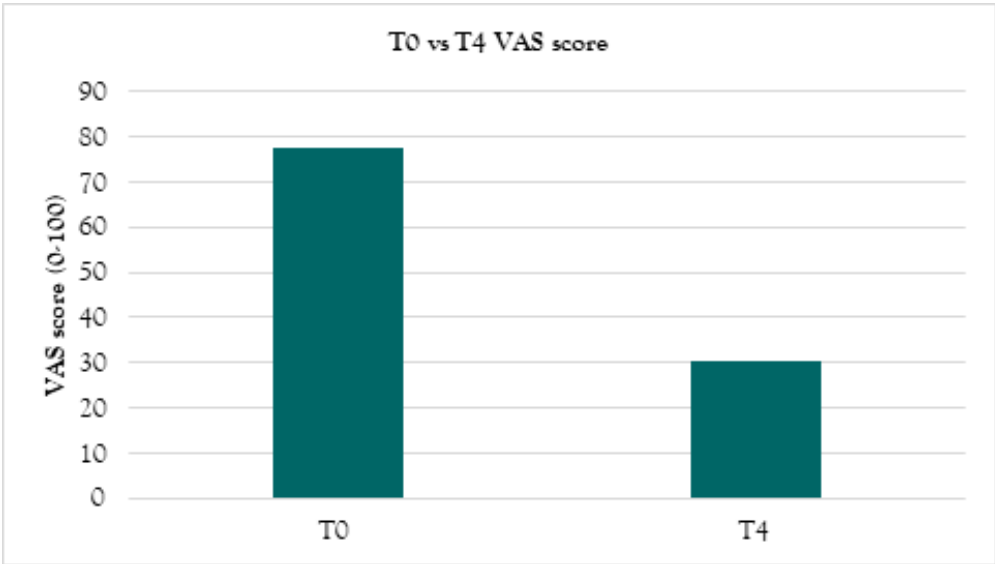

Figure 1: Reduction of mean VAS score from T0 to T4, after treatment with lipogel formulation based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, boswellia extract, glucosamine sulphate, methylsulfonylmethane (MSM) and methylsalicylate (Cibides lipogel®) three times a day for 7 days. N=60; P<0.001.

Regarding the secondary outcome we noted that overall, the gel application was well tolerated, and no adverse events were reported. Furtherly, almost all patients reported to having benefit from the treatment, in particular, 52% of patients (N=31) reported a great benefit and 45% (N=27) of patients reported a real benefit from treatment.

DISCUSSION

This study confirmed the analgesic effect of a new topical composition based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®), in 60 patients with pain caused by several musculoskeletal conditions. This new formulation was designed and studied for obtaining local relief and analgesic effect derived from the application of all active ingredients above-mentioned with strong scientific evidence already known from literature of anti-inflammatory and analgesic activity in musculoskeletal pain [8-21].

In addition to the wide list of active ingredients contained in the topical lipogel, which characterizes the final composition, it is important to note that for this product also vehicle formulation was studied *in vitro*, in order to choose between several vehicles, the better one to obtain the best characteristics of permeability and retention profile of the active ingredients in the skin [22].

CONCLUSION

The efficacy results here reported allow us to suggest a synergic effect between composition ingredients both for the improved permeability profile, and for the important analgesic effect following topical application of the gel composition. This effect was obtained relatively quickly since, already from the first applications of lipogel, patients reported statistically significant reduction in VAS scores. The topical use of the new composition here studied can represent a potential alternative to local NSAIDs use without side effects.

In conclusion, this study confirmed the analgesic effect of a new topical composition based on *Cannabis sativa* oil enriched in CBD, escin, bromelain, Boswellia extract, glucosamine sulphate, MethylSulfonylMethane (MSM) and methylsalicylate (Cibides lipogel®), in patients with localized pain related to acute minor musculoskeletal conditions.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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