Topical application of cannabinoid-based galenic preparations for pain treatment in chronic leg ulcer: case reports

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ABSTRACT

Chronic leg ulcers are disabling and often painful. Venous leg ulcers (VLU) affect mainly the elderly and represent a condition of discomfort and poor quality of life. Pain at dressing changes, for these patients, is a particularly feared and stressful procedure leading to anxiety. Topical cannabinoid treatment is an innovative treatment choice for pain modulation and reduction when treating VLU. A Canadian study showed promising results when using topical application of cannabis in patients with pyoderma gangrenous. We therefore proposed to conduct a study on cannabinoids in the management of VLU with two types of galenic preparations. Three patients were treated, with Cannabis Oil Flos (Bedrocan®) (19-22% THC; CBD<1%). The Cannabis Oil Flos showed good effectiveness in reducing painful symptoms and reducing the need for oral analgesics.

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Introduction

Chronic leg ulcers affect 1% of population, increasing to over 3.6% for those aged over 65. Women are affected 4 times more often than men. The hard-to-heal wounds are a problem of global healthcare assistance, affecting between 0.3% and 6% of older people.[1,2]

With advancing age, the increase in frequency is related to the onset of metabolic and vascular diseases.

The presence of a leg ulcer worsens the patient quality of life.[3]

Most of the ulcers are related to vascular problems; it has been reported that ulcers related to venous insufficiency are between 50-70% of leg ulcer presentation, arterial disease between 4-10%, and ulcers of mixed aetiology are 10-15%. The remaining percentage results from less common pathophysiological causes (vasculitic, hematological, dermatological, diabetic, etc.).[4]

In recent years, particular attention has been paid to the pain treatment, not only to improve the patient quality of life, but also to prevent the hemodynamic consequences of the microcirculation.

From an etiological point of view, chronic pain is classified as nociceptive (sharp, stabbing, persistent, penetrating. Responds to analgesics according to the directions WHO) or neuropatic (burning, stinging, superficial or deep, constant, or intermittent. Responds to drugs, antidepressants and anticonvulsants).

The first is prevalent in the early stages and during dressing-changes procedure. The second is characteristic

of the later phases when the nociceptive pain is not controlled and resolved. Nursing care plays an important role in pain management. The process of pain management is divided into two phases: i) pain assessment, ii) planning of healthcare interventions.

The assessment of pain has the main purpose to guide the nurses in the identification of the needs for support. The planning allows the nurse to choose the best way to achieve a full recovery of the patient's autonomy.

The optimal treatment of pain involves a preliminary phase which consist of two parts: i) the pain measurement with validated score, ii) the documantation of the scores in the medical records, accessible to all health care professionals (HCP).

Assessment tools have been developed, considering that only the patient can accurately describe his pain, while nurses and doctors often tend to underestimate the pain level, they are useful for documenting the intensity of pain perception and monitoring it over time, checking the need for interventions, evaluating their effectiveness over time and identifying any need for alternative interventions.

Measuring the pain is important in order to help alleviate the suffering.

In clinical practice we use both one-dimensional (NRS, VAS, VRS, FPS) ad multidimensional (MPQ, BPI, PAINAID) scale.

The one-dimensional scale measures only the intensity of the pain, while the multidimensional scales also evaluate other aspects of the painful sensation including sensory, affective, cognitive, and behavioural dimensions.

Pain therapy should be initiated at the lowest effective dose, in respect of the drug pharmacokinetics and pharmacodynamics, also considering the patient's age and their concomitant diseases. The dosage will be increased, if necessary, in relation to the clinical results obtained. Risks associated with the use of analgesic drugs should be contained by educating the patients and family members about their specificity and mode of administration and informing them about the possible side effects and adverse events.

In recent years, the use of opioid analgesics has become increasingly popular. The WHO provides specific guidelines for the choice of pain medication and identifies three steps based on the intensity of the pain from which the indication for the choice of the most appropriate analgesic therapy is derived:[5] i) first step: mild pain; non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants; ii) second step: moderate pain; weak opioids (hydrocodone, codeine, tramadol) with or without non-opioid analgesics, and with or without adjuvants; iii) third step: severe and persistent pain: potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with or without non-opioid analgesics, and with or without adjuvants.

Although recent studies demonstrate new and alternative approaches, the scale of the three-step WHO is still considered to be the cornerstone of the pharmacological strategy for proper pain management.

There is an increasing consensus about the flexible use of the WHO ladder and on the indication to proceed quickly to the next step in case of ineffectiveness of the therapy.

The therapeutic approach includes multidisciplinary interventions and evaluations, to define a personalized and effective diagnostic-therapeutic path.

Cannabis in pain treatment

The use of cannabis for therapeutic purposes is increasingly widespreading internationally.[6,7] Since 1998, Italian doctors are allowed to prescribe individual cannabis masterful preparations for therapeutic use (Law 08 April 1998, no. 94).

Subsequently, with the Ministerial Decree of 23 January 2013, the Ministry of Health, classified the cannabis drugs of vegetable origin, in section B of the Table of the Medicinal products.

The doctor may then prescribe cannabis products for therapeutic purposes in any pharmacy, that has the raw material and medical laboratories.

Hemp is a plant with multiple uses, and its use for medical purposes, is lost in the mists of time. Its first use dates from about 120 thousand years ago, and it is testified by the finding of seeds, resin and ashes, in a Palaeolithic site in the mountainous area of the Hindu Kush, Pakistan.

The interest in medical cannabis was rekindled in the early seventies, following the discovery of delta-9-tetrahydrocannabinol (Δ^9-THC),[8] the main psychoactive component of cannabis.

A number of new cannabinoids were separated and identified with the development of technology applied chemistry, chromatography.

Currently there are about 70 natural cannabinoids known; many of them are structural variations of the major cannabinoids and for the most part do not show psychotropic activity.

The discovery of specific receptors for exogenous cannabinoids and of endogenous molecules (endocannabinoids) that are able to activate them, simulating a large part of the typical psychotropic effects (or not) of Cannabis, has demonstrated the existence of an endogenous cannabinoid system, whose physiological role is still a matter of debate. Future studies of this system may lead to the development of new drugs with high therapeutic potential for the treatment of diseases of the nervous, immune and cardiovascular systems.

One of the most important cannabinoid is a non-psychoactive cannabidiol compound (CBD), which is able to modulate the action of Δ9-THC, prolonging its effect, strengthening the spasmolytic and analgesic effects and

limiting the psychotropic side-effects. It also shows some anti-anxiety and anti-inflammatory effects.

The CB1 and CB2 receptors are distributed in a very different way, the CB1 are mostly concentrated in the central nervous system (thalamus and cortex, but also in other structures) while CB2 ones are present substantially in the immune system cells.

The binding of the cannabinoid with CB1 and CB2 receptors causes, at peripheral level, a reduction in the secretion of various prostanoids and proinflammatory cytokines, the inhibition of protein-kinase-A (PKA) and protein-kinase-C (PKC) and of painful signal.

The analgesic properties of cannabinoids are due to the presence of CB1 cannabinoid receptors (and less of CB2 and TRPV), at central and peripheral level of the nervous system.

Rationale for the study

The protocol research started from the collaboration between the Vascular Medicine, the Wound Care Team, the Algologist and the Galenic Laboratory of S. Maria Nuova Hospital in Florence.

Our goal was to conduct a research protocol, in order to verify whether the treatment of leg ulcers using topical cannabinoid-based galenic preparations, was able to improve pain control and to reduce the use of analgesics.

The topical use has several advantages: i) does not present systemic side effects; ii) it is not invasive; iii) it can be self-administered; iv) it shows a quick analgesia.

Three patients with leg ulcers were studied. The ulcers showed some vasculitic aspects (confirmed at biopsy).

The treatment for the first two weeks was based on the application of a sodium alginate hydrogel (NU-GEL hydrogel), in which a Cannabis Flos preparation was embedded (Bedrocan®) (19%THC; CBD <1%). The hydrogel application was carried out 10-15' before dressing in order to assess the pain at dressing-change and then reapplied with a secondary dressing. The frequency of the medications was 3 times a week. However, after two weeks poor efficacy of the treatment the hydrogel vehicle for Cannabis Flos was observed and the new preparation was a Cannabis Flos Oil (Bedrocan®), 19-22% THC; CBD <1%).

The primary objective of the research protocol was to evaluate the efficacy of galenic Cannabis Flos preparations in the modulation of pain.

The secondary objectives of the protocol were: i) monitoring and evaluating the intake of analgesics; ii) improving the quality of life of the patient

Potential side effects were also evaluated.

The ulcers were open for more than 6 weeks. Exclusion criteria: patients with clinical signs and/or laboratory evidence of systemic infection, patients with known allergies to the components, pregnant women, patients with general contraindications to the use of cannabinoids, patients not able to offer adequate cooperation or to express to you personally informed consent (degenerative diseases of the CNS, cognitive impairment), patients with ABPI <0.8.

the variation of the intensity of pain reported by the patient at the beginning and during the entire duration of the study was evaluated with a VAS score.

The analgesic therapy taken by the patient (number of drugs, dosage, etc.) at the beginning and any subsequent variation were carefully analysed.

Various aspects were taken into consideration at the initial assessment (V0) and at each subsequent visit: i) population data and clinical history, relevant family history, physiological, pathological, pharmacological (only at the V0); ii) physical examination and instrumental tests; iii) pain intensity evaluation (VAS) before and after the dressing changes; iv) oral analgesic drug therapy; v) any side-effects directly referable to the therapy; vi) wound bed assessment: localization, size, characteristics, wound bed and staging; vii) wound staging; viii) pictures; ix) quality of life of the patient (verbal analysis).

This was recorded in all the visits both in the first 2 weeks of hydrogel treatment and in the second 2 weeks of oily treatment.

A form was delivered to the patients that compiled it with information about the daily VAS, the drugs taken and the feeling of health (Table 1, Figure 1).

We used a preparation of sterile sunflower oil (using the laminar flow hood), packaged in pre-measured sealed syringes, to guarantee the sterility for the use on damaged skin (Figure 2).

The results obtained in the 3 treated patients are shown below.

Table 1. Chart showing VAS, drugs taken and patient opinion (case 1, hydrogel).

Bedrocan hydrogel treatment for two weeks			
Days	**VAS**	**Drugs taken**	**Pt opinion**
1	4	Tramadol 100mg	improved
2	7	Tramadol 300mg	unchanged
3	8	Tramadol 300mg	unchanged
4	8	Tapentadol 200mg	unchanged
5	8	Tapentadol 200mg	unchanged
6	8	Tramadol 300mg	unchanged
7	9	Tramadol 300mg	unchanged
8	10	Tramadol 400mg	worsened
9	8	Tapentadol 300mg	unchanged
10	8	Tapentadol 300mg	unchanged
11	8	Tramadol 300mg	unchanged
12	8	Tramadol 300mg	unchanged
13	8	Tramadol 300mg	unchanged
14	8	Tramadol 300mg	unchanged

Case 1

Female patient with chronic venous insufficiency, obesity and smoking, ABPI>0.8.

She presented a leg ulcer in medial inferior area of the right limb with vasculitic aspects and modest exudate. The skin around the wound was erythematous with local oedema. Microbiological swab not significant.

Size: 24.0 cm2 (Figure 3). Analgesic therapy: Tramadol 100mg/day and Tapentadol 100mg/day. Previous dressing: calcium alginate.

The Bedrocan hydrogel was applied directly on the wound, and it was distributed in a homogeneous way around the wound area, and with a non-adherent dressing (Figure 4).

Compression bandage with tubular cotton, protective layer and cohesive bandage was applied.

The patient was medicated 3 times a week, as specified in the protocol.

After the first application of Bedrocan Hydrogel, the patient reported a decrease in pain and objectively a reduction of the inflammation, but, as a result of subsequent applications, the patient reported no decrease in the pain intensity.

After two weeks of treatment with the hydrogel, with a poor response probably due to the low concentration of Cannabis Flos, we started the treatment with Cannabis oil Flos 19%.

The amount of oil expected (in mL) to a dressing = 1ml x 10cmq about.

Since the first application of Bedrocan oil, the patient reported a significant pain decrease and a reduction in analgesics intake.

The data collected in the first 14 days of treatment with Bedrocan hydrogels are visible in the tab.1a. The Figure 1 shows the trend of the pain.

The VAS remained constant at a value equal to 8, and eight days after the beginning of treatment it reached a peak of 10. There had been no reduction in the use of oral pain medication. In the subsequent 2 weeks, we passed to the Bedrocan oil, with significantly better results, see Table (Table 2, Figure 5).

The application of the oily solution, since the early

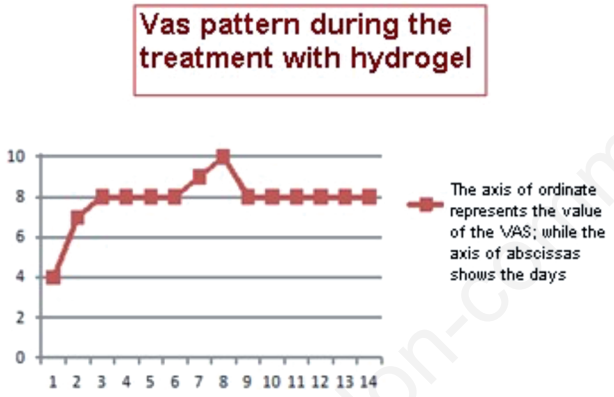

Figure 1. VAS trend (case 1, hydrogel).

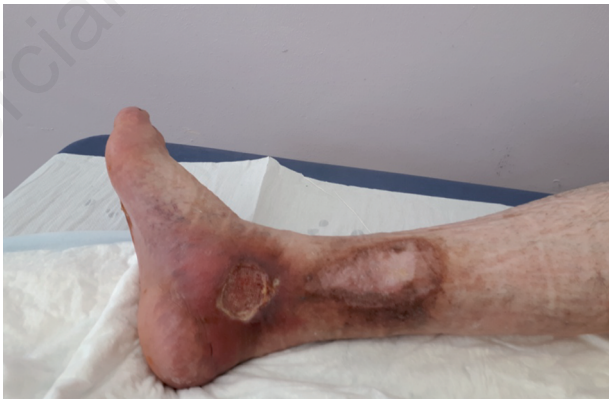

Figure 3. Case 1, ulcer picture.

Figure 2. Prepackaged ampoules.

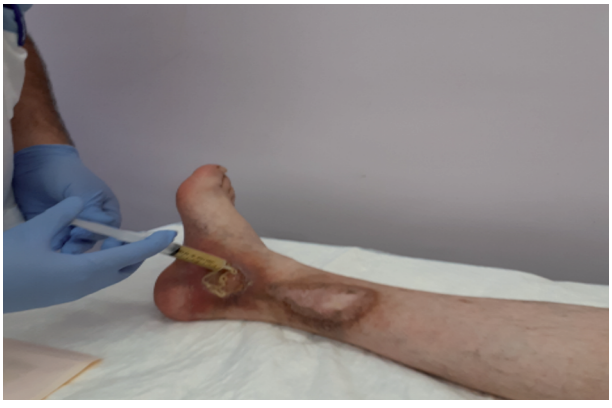

Figure 4. Bedrocan hydrogel application.

Table 2. Chart showing VAS, drugs taken and patient opinion (case 1, oil).

Bedrocan oil treatment for two weeks			
Days	**VAS**	**Drugs taken**	**Pt opinion**
15	8	Tramadol 300mg	unchanged
16	6	Tapentadol 100mg	improved
17	5	Tramadol 100mg	improved
18	6	Tramadol 100mg	improved
19	5	Tapentadol 100mg	improved
20	5	Tapentadol 100mg	improved
21	5	Tramadol 100mg	improved
22	7	Tramadol 200mg	unchanged
23	5	Tramadol 100mg	improved
24	4	Tramadol 100mg	improved
25	5	Tapentadol 100mg	improved
26	4	Tapentadol 100mg	improved
27	5	Tapentadol 100mg	improved
28	5	Tramadol 100mg	improved

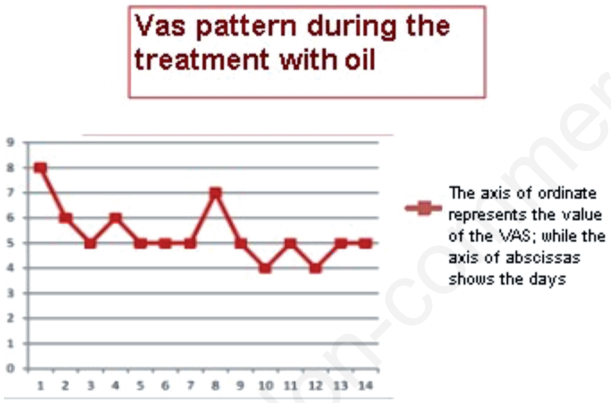

Figure 5. VAS trend (case 1, oil).

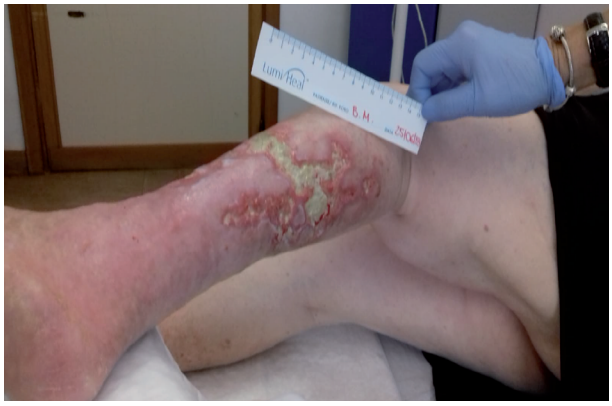

Figure 6. Case 2, ulcer picture.

days, was more effective than the hydrogel, both in terms of the modulation of pain, and drug therapy intake.

The evaluation of the pain trend, leads to the hypothesis that topical cannabis has an effect that can last for a few hours, with a slow absorption of THC by the skin. Pain at dressing-changes was not particularly affected by the oil.

Given the ineffectiveness of the hydrogel for premedication, it was decided to maintain the use of local anaesthetics, as expected by the standard protocols.

During the treatment with the hydrogel, we did not see a significant reduction in the number of analgesics consumed daily by the patient; on the contrary, during the two weeks of treatment with the oily solution, we observed a significant reduction of pain (VAS from 8 to 4 between the tenth and the thirteenth day), with a reduction in the use of drugs. The patient treated with oil reported an improvement in the quality of life, feeling better, with less pain, with an improved ambulation, and reported an improvement in carrying out daily activities.

Case 2

Patient with diabetes mellitus, rheumatoid arthritis, high blood pressure, ABPI=1

The patient had an ulcer with irregular borders and some vasculitic signs, intense inflammation around the wound, area 36 cm2, ABPI=1 (Figure 6).

Analgesic drugs: Oxycodone and Acetaminophen (5+325mg) 3cps per day. Previous dressing: hyaluronic acid sodium salt and collagenase ointment and non-adherent dressing.

After the first two weeks of Bedrocan hydrogel application, since there was no pain improvement, we started with the application of Bedrocan Oil covered with non-ad-

Table 3. Chart showing VAS, drugs taken and patient opinion (case 2, hydrogel).

Bedrocan hydrogel treatment for two weeks			
Days	**VAS**	**Drugs taken**	**Pt opinion**
1	10	Oxycodone 15mg	unchanged
2	8	Oxycodone 15mg	worsened
3	8	Oxycodone 15mg	unchanged
4	8	Oxycodone 15mg	unchanged
5	8	Oxycodone 15mg	unchanged
6	8	Oxycodone 15mg	unchanged
7	8	Oxycodone 15mg	unchanged
8	6	Oxycodone 10mg	unchanged
9	3	Oxycodone 10mg	improved
10	6	Oxycodone 10mg	worsened
11	10	Oxycodone 15mg	worsened

herent dressing for 2 weeks and continuing the bandage with tubular cotton, protection and cohesive bandage.

In Table 3 it is possible to see the results with the bedrocan hydrogel, in Figure 7 the pain trend and in the Table 4 and Figure 8 the results with the oil.

The patient reported a reduction in pain after the oil application with VAS that went from 10 to 0 after 11 days. The lesions looked more cleansed with reduced inflammation signs.

Table 4 shows a significant reduction of drug intake until the total suspension of the use of analgesics.

Case 3

The patient presented multiple ulcers in the right lower limb.

Patient on therapy with DOACs, retinal thrombosis, pulmonary emphysema.

Vasculitic ulcer with sleeve shape of the right lower limb, with red surrounding, area 47.2cm^2, ABPI=1 (Figure 9).

Drug therapy: Paracetamol + codeine (500+30mg) 3 cps per day.

Table 4. Chart showing VAS, drugs taken and patient opinion (case 2, oil).

Bedrocan oil treatment for two weeks			
Days	**VAS**	**Drugs taken**	**Pt opinion**
1	10	Oxycodone 15mg	worsened
2	8	No drugs	improved
3	7	No drugs	unchanged
4	5	Oxycodone 10mg	worsened
5	3	Oxycodone 5mg	improved
6	5	No drugs	unchanged
7	5	No drugs	unchanged
8	4	No drugs	improved
9	1	Oxycodone 5mg	improved
10	1	No drugs	improved
11	0	Oxycodone 5mg	improved
12	0	No drugs	improved
13	0	No drugs	improved
14	0	No drugs	improved

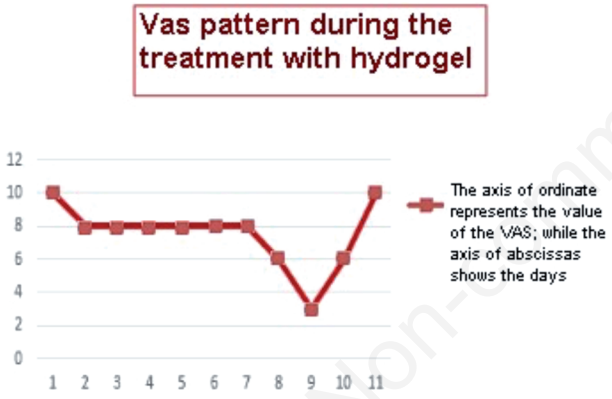

Figure 7. VAS trend (case 2, hydrogel).

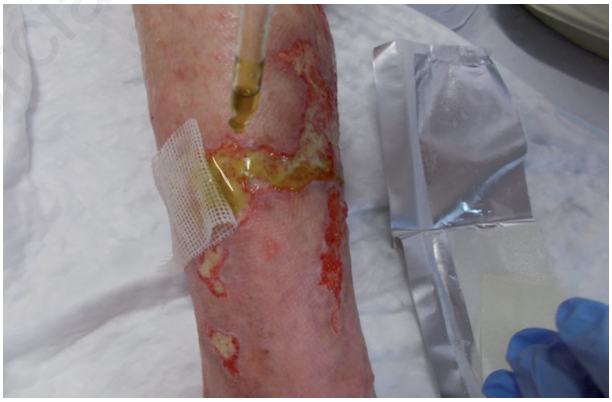

Figure 9. Case 3, Bedrocan oil application.

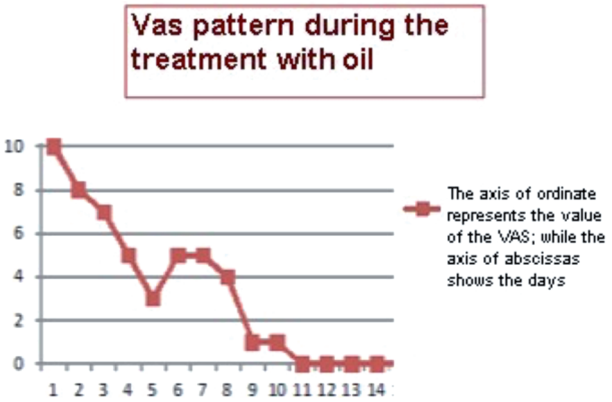

Figure 8. VAS trend (case 2, oil).

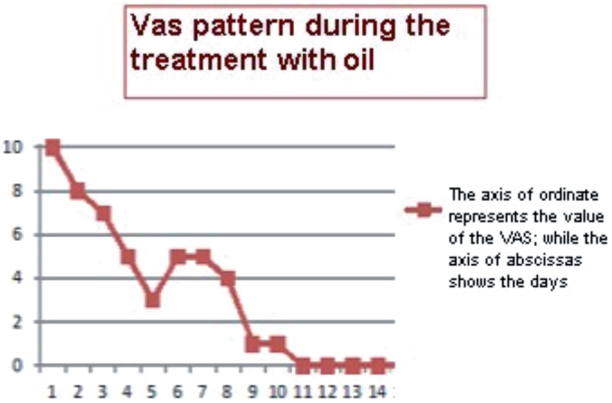

Figure 10. VAS trend (case 3, oil).

Table 5. Chart showing VAS, drugs taken and patient opinion (case 3, oil).

Bedrocan oil treatment for two weeks			
Days	**VAS**	**Drugs taken**	**Pt opinion**
1	9	Codeine 90mg	worsened
2	6	Codeine 60mg	worsened
3	7	Codeine 30mg	improved
4	7	Codeine 60mg	worsened
5	8	Codeine 60mg	worsened
6	8	Codeine 90mg	unchanged
7	7	Codeine 60mg	improved
8	6	Codeine 60mg	unchanged
9	4	Codeine 60mg	improved
10	4	Codeine 60mg	improved
11	5	Codeine 60mg	unchanged
12	3	Codeine 30mg	improved
13	3	Codeine 60mg	unchanged
14	2	Codeine 30mg	improved

The previous achievements prompted us to start the treatment directly with Bedrocan Oil.

In Table 5 and Figure 10, the data obtained from the evaluation boards are shown.

During the two weeks of treatment there was a significant reduction in the VAS (from 9 to 2) accompanied by a reduction in the intake of analgesic drugs (from 3 to 1 cp/day).

Conclusions and Discussion

The observations obtained by the research protocol has highlighted the potential action of the Cannabis Flos oil in controlling the pain in leg vasculitic ulcers.

From the analysis of the three patients treated we obtained important preliminary data that allowed us to correct and replace the initial preparation/vehicle (based on a hydrogel-based Cannabis Flos containing up to 19% THC) with the oily solution. We used a sunflower sterile oil subjected to lipophilic sterile diameter of less than ≤ 0.22micron filters.

In terms of the quality of life of patients, there was a general positive and satisfactory feedback at the end of the two weeks of treatment with the oil.

In terms of pharmaceutical expenditure, an accurate analysis of the drug economy would be interesting in larger studies to evaluate the savings resulting from the reduction of oral analgesics taken.

The reduction of the painful symptoms, found in all three patients, was accompanied by an improvement in the condition of the wound and surrounding skin.

Although there are not many similar studies in literature, and in spite of the exiguity of the sample, we obtained preliminary results that led to a similar study on a larger number of patients. It would be desirable to evaluate also the duration of the Bedrocan oil solution action for the purpose of reducing the number of medications.

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