Clinical Note

Topical Medical Cannabis: A New Treatment for Wound Pain—Three Cases of Pyoderma Gangrenosum

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Abstract

Pain associated with integumentary wounds is highly prevalent, yet it remains an area of significant unmet need within health care. Currently, systemically administered opioids are the mainstay of treatment. However, recent publications are casting opioids in a negative light given their high side effect profile, inhibition of wound healing, and association with accidental overdose, incidents that are frequently fatal. Thus, novel analgesic strategies for wound-related pain need to be investigated. The ideal methods of pain relief for wound patients are modalities that are topical, lack systemic side effects, noninvasive, self-administered, and display rapid onset of analgesia. Extracts derived from the cannabis plant have been applied to wounds for thousands of years. The discovery of the human endocannabinoid system and its dominant presence throughout the integumentary system provides a valid and logical scientific platform to consider the use of topical cannabinoids for wounds. We are reporting a prospective case series of three patients with pyoderma gangrenosum that were treated with topical medical cannabis compounded in nongenetically modified organic sunflower oil. Clinically significant analgesia that was associated with reduced opioid utilization was noted in all three cases. Topical medical cannabis has the potential to improve pain management in patients suffering from wounds of all classes. J Pain Symptom Manage 2017;54:732—736. *© 2017 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Topical medical cannabis, pyoderma gangrenosum, wound-related pain, volitional incident pain, opioid-sparing analgesia, endocannabinoid system, THC, CBD, medical cannabis oil

Introduction

Patients with wounds experience background (baseline) pain and breakthrough pain.[1,2] Wound-related breakthrough pain includes both volitional incident pain (procedural pain) and nonvolitional incident pain.[1—4] Systemically administered opioids are the commonest treatment for moderate-to-severe wound-related pain.[1,2] A wide range of topically applied agents have been studied in the wound setting including opioids (morphine, diamorphine, and methadone), ketamine, capsaicin, lidocaine, and ibuprofen.[1,2] Morphine compounded in hydrogels is the most studied wound-related topical analgesic modality with eight randomized controlled studies published.[5—7] Although it is theorized that topical opioids exert analgesia by interacting with peripherally situated opioid receptors, a degree of systemic absorption has been demonstrated, suggesting that some of the observed analgesia may be on a central basis.[7] However, the efficacy of topical morphine remains questionable as only three of the eight randomized controlled studies demonstrate analgesic efficacy.[5—7] In those studies where significant analgesia was observed, it was generally noted to have occurred within 60 minutes of its topical application.[6,7] Thus, topical morphine does not appear to be appropriate to deal with wound-related breakthrough pain. Opioid-induced inhibition of wound healing is an additional emerging concern as this has been reported with topical morphine in some animal models and one human study involving corneal lesions.[7] Furthermore, a recent longitudinal observational study of 450 patients with chronic wounds has

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demonstrated reduced likelihood of healing associated with using systemically administered opioids.[8]

Reports of the use of extracts from the cannabis plant being applied topically to open cutaneous wounds, for the purposes of promoting wound healing and relieving wound-related pain, date back to antiquity. Preclinical animal models, two of which involved the radiant heat tail-flick test and one employing mustard-induced corneal lesions, have demonstrated significant peripherally mediated antinociception using the synthetic cannabinoid agonist WIN55,212−2 (WIN-2) applied topically.[9−11] The results of one study also suggests a possible interaction and potentiation between cannabinoid and opioid nociception at a peripheral level.[10] Many industrialized countries have legalized botanical cannabis and its extracts for medical purposes. Medical cannabis (MC), also known colloquially as "medical marijuana," must be distinguished from recreational cannabis as it intends to relieve pain and other symptoms and potentially modulate diseases, as opposed to intending to deliver a psychotomimetic state of "high."[12] The most clinically relevant components of MC are the cannabinoid agents delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) and the non-cannabinoids compounds, terpenoids, and flavonoids.[12] MC may be dispensed in dried botanical format that may be smoked, vaporized, or consumed as edibles. MC extracts, such as those compounded in organic oils, may be administered orally or applied topically.

Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic skin disease.[13−16]Although 50−70% of cases occur in the setting of inflammatory arthritis, inflammatory bowel disease, hematologic diseases, and solid neoplasms, the remainder are idiopathic.[13−16] Classically, it presents as cutaneous ulcerations that most commonly occur on the lower extremities.[13−16] PG represents a significant challenge from both diagnostic and therapeutic perspectives. PG is frequently misdiagnosed as cellulitis, venous leg ulcers, and arterial ulcers. Pain is a universal symptom of PG and most patients suffer high levels of pain that is often refractory to high-dose systemically administered opioid analgesics. Because the lesions of PG tend to be chronic and relapsing, they have the potential to substantially compromise quality of life over a protracted period.

Methods

Before the initiation of topical medical cannabis (TMC), all patients underwent a complete medical workup and providing informed consent for the use of this experimental treatment. All patients were also subjected to wound biopsies for histopathology and immunoflourescence studies to rule out other pathologies. For all three cases, patient reported average daily pain scores, based on an 11-point numeric rating scale (0−10), and average daily opioid use (morphine sulfate equivalents in mg/day) were assessed before and after initiating treatment with TMC. Using a paired t-test, the mean pre-TMC average daily pain score was compared with the mean post-TMC value for all three cases. The percent decrease in average daily pain score after the initiation of TMC was also determined for each case. For average daily opioid dosage, a paired t-test was used to compare the mean pre-TMC morphine sulfate equivalents (MSE) used to the mean post-TMC values for cases 1 and 2 only. In Case 3, the mean MSEs used was nil both before and after initiating treatment with TMC, precluding comparison with a paired t-test. For all hypothesis testing, a P-value <0.05 was considered significant and a decrease in average pain score greater or equal to 30% was accepted to be clinically significant. All statistical analyses were carried out using GraphPad QuickCalcs Software (GraphPad Software Inc., La Jolla, CA).

Case 1

A 50-year-old woman presents with a painful left medial leg ulcer of at least 12 months' duration (Fig. 1). This PG was superimposed on an area of lipodermatosclerosis resulting from a post-phlebitic syndrome in the setting of Factor V Leiden deficiency. She was initially treated with systemic corticosteroids, intralesional corticosteroids, opioid analgesics, and inelastic compression systems. In view of her continued high levels of pain, she agreed to a trial of topical MC oil (ARGYLE™ THC

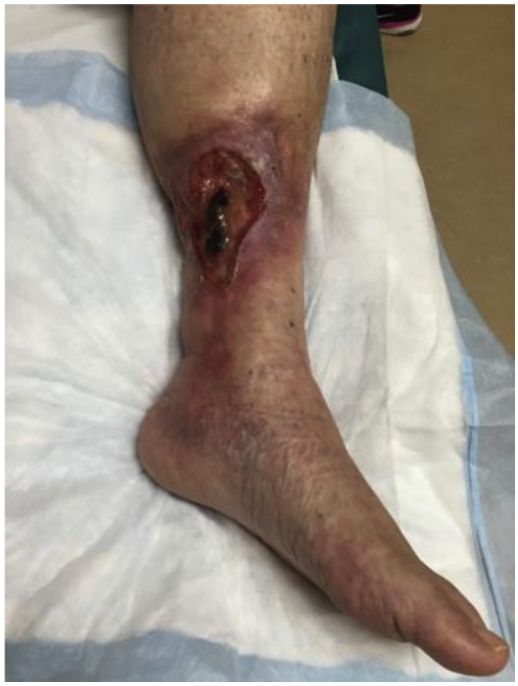

Fig. 1. Case 1.

5 mg/mL + CBD 6 mg/mL) from TWEED Inc (Ontario, Canada). One milliliter of TMC was applied to wound bed daily followed by application of inelastic compression bandaging. The use of the multilayered inelastic compression system precluded the use of TMC for breakthrough pain in this case. After the initiation of TMC, she did not require further corticosteroids.

Case 2

A 76-year-old man, with no concomitant illnesses, presents with the first-ever occurrence of a painful right lateral ankle ulcer (Fig. 2). He was prescribed opioid analgesics and systemic corticosteroids both before and after the initiation of TMC. Before initiating TMC, he was also administered intralesional corticosteroids. He continued to experience high levels of pain and, thus, he agreed to a trial of MC oil (Bedrolite™ THC 7 mg/mL + CBD 9 mg/mL) from Bedrocan Inc. He applied 0.5−1.0 mL of MC oil to the wound bed two times per day plus one to three times daily for breakthrough pain. The wound with dressed with nonadherent dressings.

Case 3

A 60-year-old woman with systemic lupus erythematosus presents with a recurrent painful right lateral leg ulcer (Fig. 3). She was prescribed systemic corticosteroids both before and after the initiation of TMC. She had a history of side effects with opioid analgesics and, thus, refused to use them. She used acetaminophen 325−650 mg q6h prn for pain. Given her high levels of pain, she agreed to a trial of MC oil (Bedrolite THC 7 mg/mL + CBD 9 mg/mL) from Bedrocan Inc. She applied 0.5−1.0 mL of MC oil to the wound bed two times per day plus one to three times daily for breakthrough pain. The wound was dressed with nonadherent dressings.

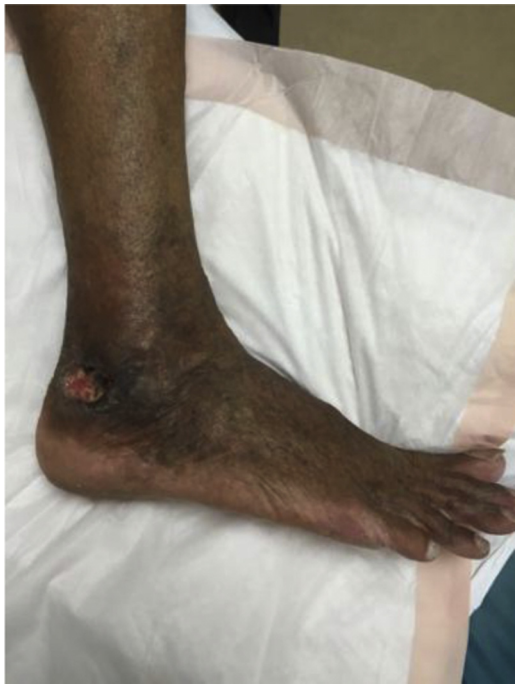

Fig. 2. Case 2.

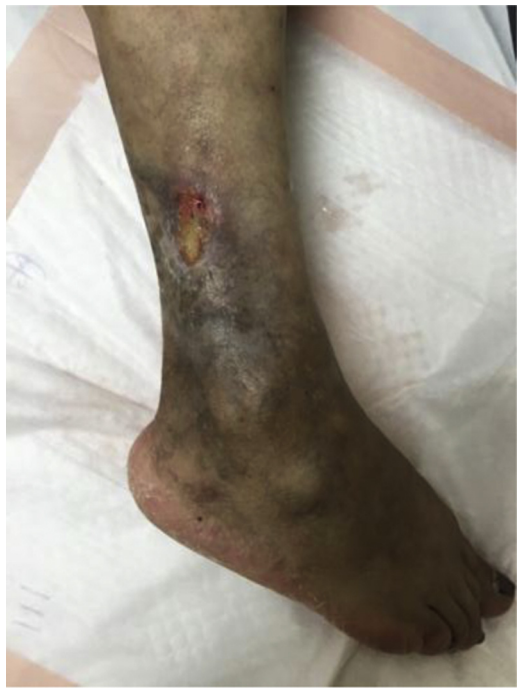

Fig. 3. Case 3.

Results

The data in Tables 1 and 2, collected prospectively, reflect clinical observations over a total of 17, 21, and 12 weeks for cases 1−3 pre-TMC, respectively, and over 33, 9, and 21 weeks for cases 1−3 post-TMC, respectively. Each of the three patients reported consistently experiencing the onset of analgesia within three to five minutes of each application. After the initiation of treatment with TMC, there was a statistically significant ($P < 0.05$) decrease in the average daily pain score in cases 1 and 2 (Table 1). In addition, all cases demonstrated "clinically significant" pain reductions of greater than 30% which is the generally accepted threshold quoted in international pain research.[17] In Case 1, the mean pain score decreased from 8.25 to 2.76, a 66.5% decrease that is both clinically and statistically significant ($P = 0.0007$). For Case 2, the pre-TMC mean pain score was 8.75, which decreased by 73.4% to 2.33, a clinically and statistically significant ($P = 0.0006$) change. Finally, for Case 3, the mean pain score decreased from 4.29 to 1.50, a 65% change that was clinically significant but did not quite reach the threshold for statistical significance ($P = 0.0720$). The average daily opioid dose in

Table 1
Comparison of Mean Daily Pain Scores Before and After Initiating Treatment With TMC

Case	Mean Daily Pain Score Pre-TMC ± SD (*n*)	Mean Daily Pain Score Post-TMC ± SD (*n*)	*P*-Value	Percent Change (%)
1	8.25 ± .50 (4)	2.76 ± 1.34 (25)	0.0007	66.5
2	8.75 ± .46 (8)	2.33 ± 1.97 (6)	0.0006	73.4
3	4.29 ± .95 (4)	1.50 ± 1.60 (7)	0.0720	65.0

TMC = topical medical cannabis.

cases 1 and 2, measured as MSE (mg), decreased in a statistically significant manner after starting the application of TMC (Table 2). For Case 1, the mean MSE decreased from 26.00 to 0.24 mg, a statistically difference ($P = 0.0013$). In Case 2, mean MSE decreased from 27.33 mg to 12.50, a decrease that was also statistically significant ($P = 0.0001$).

Discussion

To our knowledge, this is the first published human case report of topical cannabinoid therapies achieving analgesia that was clinically significant, statistically significant in two of the three cases, and opioid sparing in the setting of PG. TMC improved baseline pain levels in all cases while also being effective for breakthrough in the two cases where it was used in this capacity. Of note, the two cases demonstrating statistically significant changes in pain scores also had very high mean daily pain scores before starting TMC treatment, suggesting potential for increased efficacy in patients suffering from more severe pain. Although not yet fully elucidated, the clinical utility of MC may be largely explained through the interaction of cannabinoids and non-cannabinoids, which intrinsically possess analgesic and anti-inflammatory properties, with the human endocannabinoid system.[12] The endocannabinoid system is ubiquitous throughout the human body and is composed of at least two receptor types (CB1 and CB2), endogenous ligands, and associated degradation pathways.[12] The skin, its adnexal components, and subcutaneous tissues are rich in cannabinoid receptors making them logical and viable targets for therapies based on MC.[12,18] Unlike intact skin which is polar and hydrophilic, wounds lack epithelial coverage and are nonpolar and lipophilic. Therefore, lipophilic compounds, such as the cannabinoids THC and CBD, may be readily absorbed through all classes of cutaneous wounds.

Table 2
Comparison of Mean MSE Before and After Initiating Treatment With TMC

Case	Mean MSE (mg/day) Pre-TMC ± SD (*n*)	Mean MSE (mg/day) Post-TMC ± SD (*n*)	*P*-Value
1	26.00 ± 5.16 (4)	0.24 ± .88 (25)	0.0013
2	27.33 ± 2.18 (8)	12.50 ± 1.23 (6)	0.0001
3	0 (4)	0 (7)	n/a

MSE = morphine sulfate equivalents; TMC = topical medical cannabis; n/a = not applicable.

The analgesic outcomes observed in this case report are congruent with the results of a recently published case of a painful malignant wound that responded to TMC.[19] Moreover, the analgesic potential of cannabinoid therapies is supported by a recent systematic review and meta-analysis[20] and updated guidelines published by the Canadian Pain Society.[21]

The opioid-sparing effect observed in this case report cannot be overemphasized in view of the current global crisis related to opioid overuse and accidental deaths from overdoses.[22] Thus, any measures that can improve analgesic outcomes while reducing opioid utilization should be strongly considered.

In summary, this is the first case series to demonstrate the potential for TMC to provide effective analgesia that was opioid sparing in the setting of PG. The rapid onset of analgesia after topical application suggests that the effects were mediated through absorption of the cannabinoids THC and CBD that subsequently interacted with cannabinoid receptors expressed on peripheral nociceptors and immune cells. The authors recognize the limitations of the small sample used in this preliminary investigation, which limits the evaluation of efficacy and safety. However, the promising reported findings indicate that TMC warrants further investigation through large and controlled trials in PG and all other wound classes.

Disclosures and Acknowledgments

The authors declare no conflicts of interest.

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