Clinical Note

Treatment of Painful Skin Ulcers with Topical Opioids

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Abstract

Recent research suggests that opioid receptors on peripheral nerve terminals may play an important role in the modulation of pain. Clinical applications of this knowledge have been rather slow to evolve. We describe a consecutive series of nine patients with painful skin ulcers due to a variety of medical conditions. All patients were treated with a topical morphine-infused gel dressing. Seven of the nine patients experienced substantial and another experienced a lesser (but still significant) degree of analgesia. The ninth reported no relief, but his wound was not an open ulcer. Discussion centers on the practical application of this development in the large number of patients with painful skin lesions. J Pain Symptom Manage 1999;17:288–292. *© U.S. Cancer Pain Relief Committee, 1999.*

Key Words

Pressure ulcer, decubitus ulcer, receptors, opioid, peripheral nerves, pain, administration, topical

Introduction

It has long been known that opioid analgesics relieve pain through their action on the central nervous system. More recent research has suggested that they also may produce effective analgesia through action at peripheral sites. That is, opioids may successfully modulate the experience of pain by binding to opioid receptors on sensory nerve terminals located at the periphery. The bulk of the theoretical work in this area has been conducted by Stein and colleagues.[1] These investigators have conducted a series of studies, primarily in rats, demonstrating that the application of exogenous opioid agonists to areas that are inflamed produces significant analgesia.[2]

The use of topical opioids for skin ulcer analgesia bears great potential. If the theories about the mechanism of action of topical opioids are correct, it should be possible under appropriate conditions to achieve analgesia with few (if any) of the usual opioid-related side effects. Theoretically, it should be possible to apply extremely small doses of opioids to wounds while achieving significant analgesia with little or no systemic absorption. As a result, patients may achieve superior analgesia, have fewer systemic medications to take (thus increasing treatment adherence), and reduce or eliminate the risk of comorbidity related to constipation, sedation, cognitive slowing, and nausea.

Two reports in the literature address the use of analgesic substances applied topically to painful skin lesions in humans. In the first, Jepson[3] reported the use of an aqueous-based

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cream containing 3% benzydamine (a nonsteroidal anti-inflammatory drug) for pain due to pressure sores. Seventeen patients entered the study, with a total of 30 distinct sores. After 24 hours of treatment, 29 of the 30 ulcers were pain-free, with complete pain relief achieved in all 30 by 48 hours. The second[4] reported utilization of a mixture of 10 mg diamorphine in an unspecified amount of IntraSite gel, applied daily to two decubitus ulcers and one malignant skin ulceration in three patients. All patients reported being more comfortable after the first application, with the benefit lasting throughout the day. One patient with an equivocal response was switched to an opioid-free gel for a second day, with a significant recrudescence of pain. On Day 3, the diamorphine was again added to the gel, with noticeable analgesia. Two patients were treated for less than a week because their general health deteriorated, but the other was treated for 2 months.

We report a consecutive series of cases treated with morphine-infused IntraSite gel (MIG). Nine individuals have received this treatment. Eight of the patients were successfully treated with seven reporting a significant decrease in pain. One additional individual reported a lesser degree of pain relief; the final patient reported no noticeable change in his level of pain. All of the patients had serious comorbid conditions, and most had pain from more that one site. We attempted to differentiate pain due to ulcers from pain of other etiologies. This was an open-label treatment, and no attempt was made to create a blind.

After review of the case report by Back and Findlay,[4] and researching the type of gel that they used, we calculated an equianalgesic dose of morphine and infused it into IntraSite gel to obtain a 0.1% weight-to-weight (w/w) solution. (IntraSite is the standard gel currently in use at our institution for dressing decubitus ulcers.) The gel is spread on the ulcer after cleansing, and a clean 4 × 4 gauze dressing applied. Alternatively, the gel is applied to the 4 × 4 gauze dressing, and it is firmly applied to the wound so that it is in direct contact with all exposed wound surfaces.

Case Reports

All patients treated with this MIG regimen were first seen by the Cancer Pain Management Service (CPMS) on referral from other services. In most cases, the finding of painful skin lesions was incidental to the reason for referral, and was uncovered in the course of a thorough pain assessment. Only Case 5 was referred specifically for the treatment of painful skin lesions, as a result of our success with Case 1.

Case 1

Patient A, a 36-year-old white female with a history of Crohn's disease and chronic ulcers due to pyoderma gangrenosum, had skin grafted from her right hip and buttock to the right arm for a wound that would not heal. She presented to the emergency room because of pain at the graft site at 1, 5, 7, and 14 weeks after the skin graft. Throughout these 14 weeks, Patient A was noncompliant with home health care because of the pain associated with dressing changes. She had been taking oxycodone/acetaminophen for pain management with little relief. She was finally admitted for pain management and malnutrition. Medications prescribed during the first week after admission included prednisone, ketorolac (30 mg intramuscularly [IM] every 6 hours), amitriptyline (50 mg at bedtime), and tramadol (50 mg every 6 hours), all reported to inadequately control the pain. The patient refused dressing changes on the third and fourth hospital days, allowing it on the fifth, with resultant severe pain. On the seventh day, psychiatry was consulted due to the primary team's concern that her frequent requests for analgesics indicated an underlying substance abuse disorder. The consultant's (one of the authors, T.D.L.) impression was not of substance abuse, but of poorly controlled pain, and MIG 0.1% w/w concentration (approximately 1 mg morphine/1 ml IntraSite gel) was recommended BID at dressing changes. After the first application, the patient reported that the pain relief was tremendous, and she ambulated throughout the hospital without difficulty or pain. The next day, the patient began eating well, and her requests for oral analgesics decreased. She began sleeping better and no longer refused dressing changes. The patient continued to improve throughout the course of the hospital stay, and on the thirteenth day she was discharged with MIG to apply topically to the wounds twice a day. Amitriptyline, prednisone, and tramadol were continued at their previous doses. Patient

A continued to use the MIG for 2 weeks after discharge, when the dermatology service recommended a change in the dressing regimen to silver sulfadiazine, rather than IntraSite gel.

Case 2

Patient B, a 45-year-old white male, was admitted to the hospital for treatment of symptoms related to esophageal cancer. He was being treated with oral and transdermal opioid analgesics at the time of admission, and due to esophageal pain his opioids were increased. Pain was not well controlled, and finally a morphine infusion was started and titrated to comfort. Other medications included nortriptyline (50 mg at bedtime), and alprazolam, used on an "as-needed" basis (a long-term medication for this patient). The CPMS was consulted for management of severe pain due to a sacral decubitus ulcer. This patient was able to distinguish pain from different sites, making use of the gel evaluable. MIG 0.1% w/w concentration was recommended, and applied BID at dressing changes. Throughout the remainder of his 15-day hospital stay, no further pain was reported at the ulcer site, although pain from other sites continued to require opioid management.

Case 3

Patient C, a 67-year-old white male, was admitted to the hospital with widely metastatic renal cell carcinoma. He was suffering from low back pain (due to lumbar cord compression), as well as pain at the site of a sacral decubitus ulcer. The CPMS was consulted and a comprehensive treatment plan established. In addition to oral opioids (which were helpful for the back pain but did not relieve the ulcer pain) and a trial of amitriptyline, the patient was treated with MIG 0.1% w/w concentration BID at dressing changes. Prior to application of the gel, pain at the ulcer site was reported by the patient as 6.5 on a scale of 0–10. Three, 6, and 13 hours after the first application, the patient reported his pain to be 0. The wound remained pain-free for 45 hours. Discomfort was reported at that time, when the affected area was being cleaned for extensive diarrheal stool. MIG was applied after the dressing change, and pain returned to 0. Treatment continued with similar results through discharge.

Case 4

Patient D, a 78-year-old white female, was admitted to the hospital with stage IV ductal carcinoma of the right breast. The tumor was a large (measuring 2.5 by 2.5 inches) ulcerated lesion, leaking serosanguinous fluid. The CPMS was consulted for management of pain including pain from bony metastases and that of this lesion. In addition to treatment with IV opioids (which had to be discontinued due to excessive sedation and substituted with more judicious use of oral opioids) and nonsteroidal anti-inflammatory drugs, treatment with MIG 0.1% w/w concentration was recommended. Prior to application, pain at the tumor site was reported between 6 and 10 on a scale of 10. After application, there were no reports of pain at the ulcer site during the remainder of her 8-day hospitalization.

Case 5

Patient E, a 49-year-old white female with a foot ulcer due to diabetes mellitus, complicated by peripheral vascular disease, was also treated with MIG, 0.1% w/w concentration, with good pain relief reported for over 6 months. After 6 months, the patient reported that she was achieving less-than-optimal analgesia with each application. This may have been due to an extension of her wounds. Consequently, the morphine concentration was increased to 0.15%. Good pain control again was achieved, and the patient remained on this regimen for more than 1 year.

Case 6

Patient F, a 31-year-old white female, was being followed by the CPMS for severe low back pain. She had a prior history of hydradenitis suppurativa (HS) and during her course had a severe outbreak. At the time of her outbreak, her back pain had stabilized, and the pain from the HS lesions was reported as 8 out of 10. MIG was applied at 0.15% w/w concentration, approximately 1 ml to each site (1.5 mg of morphine per dose; this higher concentration was used because it was readily available in the pharmacy due to its concurrent use by Patient E). Analgesia onset was noted by the patient at 15 minutes, and continued until the pain rating reached 0/10. Pain remained 0/10 until the next dressing change 12 hours later. The patient continued BID dressing changes until the lesions healed, with pain maintained at 0/10.

Case 7

Patient G, a 48-year-old white female seen on an outpatient basis for management of painful melanoma lesions on her foot and lower leg, was treated on an "as needed" basis with MIG 0.1% w/w concentration. She reported that each application of the MIG produced significant pain relief, although this relief lasted only a couple of hours. She continued to use the MIG on an "as needed" basis for over a year, until the time of her death from progressive melanoma. The CPMS had not been consulted, and no pain ratings were obtained.

Case 8

Patient H, a 51-year-old white male with a long history of multiple sclerosis, had been bed-bound for the past few years. The CPMS was consulted for management of pain resulting from a large sacral decubitus ulcer. Plastic Surgery recently had performed a transverse rectus abdominis myocutaneous (TRAM) flap procedure for that ulcer. In addition to the pain at the surgical site, the patient complained of significant pain due to Stage I skin ulcers located on both of his scapulae. Efforts to titrate opioids above the level of a 25 μg/hr fentanyl patch produced clinically significant respiratory depression. The patient reported that the fentanyl patch produced adequate pain relief at the site of his sacral wound, but rated the pain at the scapular sites as 7/10. MIG in a 0.15% concentration was recommended (again, due to ready pharmacy availability), and applied twice a day to the scapulae at dressing changes. Patient H's pain at the scapular sites was reduced to a level of 1 to 2/10 following MIG treatment. The patient continued with this treatment for 6 weeks, with continuing successful analgesia.

Case 9

Patient I, an 81-year-old white male with colorectal cancer, was given 0.1% MIG for relief of pain related to swelling, redness, and bruising on his scrotum. The patient reported no detectable change in his pain level. It should be noted that this patient had no open wound, a factor that may have contributed to the lack of efficacy. In addition, there is no evidence that there was any inflammation.

None of these nine patients has reported somnolence, skin irritation, or other side effects from the use of the gel, nor has wound healing been slowed noticeably. In fact, in patients for whom pain had caused nonadherence to wound care procedures, healing was improved.

Discussion

Certain patient groups clearly are at an elevated risk of developing skin ulcers. For instance, Richardson and Meyer[5] reported that 60% of the hospitalized quadriplegic patients in their survey had pressure ulcers. Versluysen[6] reported a 66% incidence of pressure ulcers among elderly patients admitted for femoral fracture. Based on the estimated population of pressure ulcer sufferers reported by Miller and Delozier[7] and a study of the prevalence of pain among pressure ulcer patients,[8] there may be as many as 21,000 hospital inpatients suffering significant pain from pressure ulcers each year. It is harder to determine the number of nursing facility and home care patients with painful pressure ulcers, but it seems safe to say that the number is as large as or larger than the number of hospital inpatients. Thus, there may be as many as 40,000 Americans each year who could benefit from an intervention to reduce the pain associated with their pressure ulcers.

Identified pressure ulcer risk factors include advanced age, immobility, decreased body weight (or malnutrition), dry skin, incontinence, and lymphopenia.[9–12] Other conditions associated with the development of painful skin lesions include diabetes mellitus, peripheral vascular disease, severe Kaposi's sarcoma lesions in people with AIDS, and cutaneous lesions related to melanoma and other cancers. Because comorbid conditions can predispose patients to opioid toxicity, achievement of significant analgesia without the use of systemic opioids may be greatly beneficial. In fact, there is extremely little information available in the scientific literature regarding the incidence and prevalence of, and effective treatments for, painful skin lesions. In our experience, systemic opioids are only marginally effective for most of these lesions, and are replete with problematic side effects. Aside from pressure ulcers, virtually any other group of individuals with painful skin lesions of any etiology may benefit from this application, should it be shown to be effective.

Our case series demonstrates a remarkable

degree of efficacy with respect to analgesia in this population. The only patient reported to have an equivocal response may well have been an inappropriate candidate for the treatment, due to the absence of significant inflammation. All other patients responded rapidly and achieved total or nearly total pain relief with the first application of the MIG. Although it is difficult to summarize the amounts of systemic opioids used by these patients during the MIG treatment course (because of frequent titration to control other painful symptoms and variable use of "as needed" dosing for breakthrough pain), it is notable that all except Case 1 (Patient A) were taking systemic opioids at the time of MIG treatment initiation, with doses ranging from minimal to continuous infusion rates of up to several mg/hour. Despite longstanding use of significant doses of systemic opioids, the application of no more than 5 mg of morphine to these painful skin lesions produced up to 12 hours of analgesia. It seems safe to say that similar doses administered systemically should have had no-to-minimal effect on this pain, and certainly would not have lasted for 12 hours. These facts suggest a mechanism of action that differs greatly from that seen with systemic administration. We believe that the model of peripheral opiate receptors is the best available explanation of these results.

We feel that this represents a promising area for further research, one that could benefit a significant population of patients. The animal studies done thus far indicate that the presence of inflammation is critical to sprouting of peripheral nerve terminals at the site of injury, and the recruitment of opioid receptors. It is as yet unclear whether the intensity of inflammation may alter the level of recruitment and subsequent response to topically applied opioids. Our patients included those with obvious inflammatory components as well as some with less distinct inflammation. Clearly, in the one patient with intact skin and no real inflammation, no response could be observed. It would be valuable to study this application both in series with similar wounds, as well as comparing for response in different wound types. Further research, including a double-blind, placebo-controlled study of MIG for skin ulcers, needs to be conducted. Such research could help clarify issues such as the time to analgesia onset and duration of pain relief, the degree of systemic opioid absorption, and the site of opioid action (i.e., peripheral vs. central). Additional research to demonstrate the efficacy of opioids other than morphine, and to determine the impact (if any) on wound healing should be pursued, as well.

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