Analgesic effect of topical sevoflurane on venous leg ulcer with intractable pain

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Keywords
Pain intractable, drug therapy, varicose ulcer, drug therapy, anesthetics, inhalation, therapeutic use, sevoflurane

Summary
We are presenting the case of a patient with a very painful venous ulcer for whom therapy with different analgesic combinations (including acetaminophen, metamizol, tramadol, morphine, fentanyl, buprenorphine, pregabalin, gabapentin, as well as applications of lidocaine/prilocaine eutectic cream and infusion of epidural ropivacaine) was unsatisfactory. Analgesic control was finally achieved through applications of liquid sevoflurane to the wound, which resulted in immediate, intense, and long-lasting analgesia. To the patients satisfaction, the same response was obtained throughout the 16 days it took the ulcer to heal. The compassionate use of sevoflurane in this innovative and promising manner warrants further research to evaluate its efficacy and safety.

Schlüsselwörter
Therapieresistente Schmerzen, medikamentöse Therapie, Ulcus cruris, Anästhesie, Inhalation, therapeutischer Nutzen, Sevofluran

Zusammenfassung
Wir stellen den Fall eines Patienten mit einem sehr schmerzhaften venösen Geschwür vor, bei welchem die Therapie mit verschiedenen Schmerzmittelkombinationen (einschließlich Paracetamol, Metamizol, Tramadol, Morphin, Fentanyl, Buprenorphin, Pregabalin, Gabapentin, sowie der lokalen Anwendung von Lidocain/Prilocain Creme und epiduralen Infusionen mit Ropivacain) unbefriedigend war. Schmerzstillende Kontrolle wurde schließlich erreicht durch direkte Anwendung von flüssigem Sevofluran auf der Wunde, die zur unmittelbaren, intensiven und lang anhaltenden Analgesie führte. Zur Zufriedenheit des Patienten wurde eine ähnliche Reaktion während des Zeitraums von 16 Tagen erreicht, in dem das Geschwür heilte. Die direkte/topische Anwendung von Sevofluran mit dieser innovativen und vielversprechenden Methode rechtfertigt weitere Untersuchungen zur Bewertung der Wirksamkeit und Sicherheit von Sevofluran.

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Venous ulcers are a major health issue. Besides their financial impact (1), a significant part of this issue stems from the pain associated with these ulcers. There is a percentage of patients who suffer intractable pain resulting in poor quality of life (insomnia, immobility, irritability), not to mention the adverse effects that may arise from these therapies (2, 3). Therefore, a new alternative in analgesia would be welcome.

Sevoflurane (Sevorane®) is a halogenated inhalation anesthetic agent that has been used in general anesthesia for decades and, over this period of time, has proven to be a very safe drug (4, 5). In addition to its hypnotic effect, its profile as an analgesic is being determined, particularly in spinal applications (6, 7).

The following is a description of our first experience with the compassionate use of liquid sevoflurane as a topical irrigation in the analgesic management of intractable pain in a case of venous ulcer.

Clinical case

The patient was a 76-year-old woman with main antecedents of arterial hypertension, chronic atrial fibrillation diagnosed 4 years ago when patient suffered from a deep vein thrombosis of the left lower extremity.

She was admitted to Vascular Surgery for intense pain uncontrolled with several analgesics (acetaminophen, tramadol, pregabalin, morphine) associated to a necrotic left external maleolar ulcer, ischemic etiology being ruled out by the ankle-brachial index. Epidural infusion of ropivacaine and fentanyl plus topical application of lidocaine/prilocaine eutectic cream (EMLA®) controlled resting pain, but they were insufficient to allow tolerance to vacuum-assited closure (VAC) therapy. Besides, the patient suffered blockage of the rigth lower extremity, and finally the epidural catheter was removed on patient request. The patient was discharged with pregabalin, morphine and transmucosal fentanyl, with regular dose increments because of the pain was still poorly controlled.

In this context, she was readmitted to the Internal Medicine service with diagnoses of opioid poisoning, prerenal acute renal failure, and intractable painful ulcers of the lower extremities. Following initial

clinical improvement in her general condition, the pain again became the primary problem, despite analgesic therapy with transdermal buprenorphine and sublingual buprenorphine tablets for rescue analgesia, and the patient was transferred back to Vascular Surgery.

Upon examination, two supramaleolar ulcers were noted on the posteroexternal surface of the distal third of both legs, the left also having exudate and clinical signs of superinfection (▶Fig. 1). Ischemic etiology was ruled out based on preserved plethysmographic curves and normal ankle-brachial index (left 0'93, right 0'86). Bilateral venous ultrasound study performed on deep venous system and mayor saphenous veins showed important venous reflux (duration higher than 3 seconds and speed equal to 35 cm . sec-1). Histologic study was not performed. These findings strongly supported the venous etiology for both ulcers, and the patient was diagnosed of chronic venous insufficiency (class 6 of CEAP classification).

Right ulcer pain was adequately controlled, numerical pain scale (NPS) <4/10, but pain from left ulcer was severe, NPS = 8/10. This pain was interfering with the patient's rest at night, and she was in a very bad mood. Furthermore, local treatments to the left leg ulcer were so painful that the patient was refusing them. Reinsertion of an epidural catheter was offered to the patient, but this she also refused because of her previous bad experience.

In this desperate context the patient was offered the compassionate use of local sevoflurane irrigations in an attempt to control the pain. Permission for the off-label use of sevoflurane in this particular patient was obtained from the Pharmacy Department and from the authorities of our institution. The patient gave us written consent to undergo an initial trial application on the more painful left leg ulcer, with the option to have the application repeated if the result was satisfactory. The first treatment consisted of removing the macroscopic debris using a normal saline-humidified gas and irrigating the ulcer bed with 5 ml of liquid sevoflurane. The patient reported an immediate feeling of coolness and then, about 2 minutes later, intense analgesia (NPS = 4/10) that lasted for a period of about 12 hours before returning to the pretreatment score (NPS = 8/10). During the period of analgesia, the patient was able to rest and sleep. After this, the patient herself requested that the sevoflurane treatments be repeated daily, which lasted 16 days. The only undesirable effect that appeared was a mild pruriginous irritation of the healthy skin around the wound, which could be minimized by keeping the sevoflurane confined within the wound edges. Even so, the patient's subjective degree of satisfaction was very high.

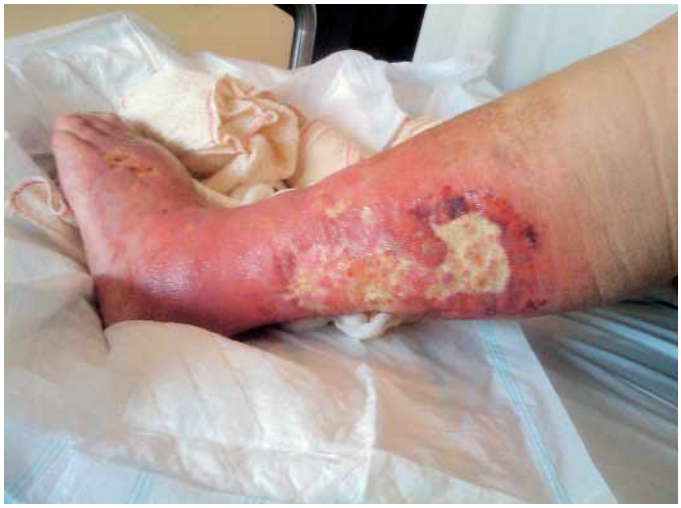

Fig. 1
Venous ulcer prior to initiating sevoflurane applications.

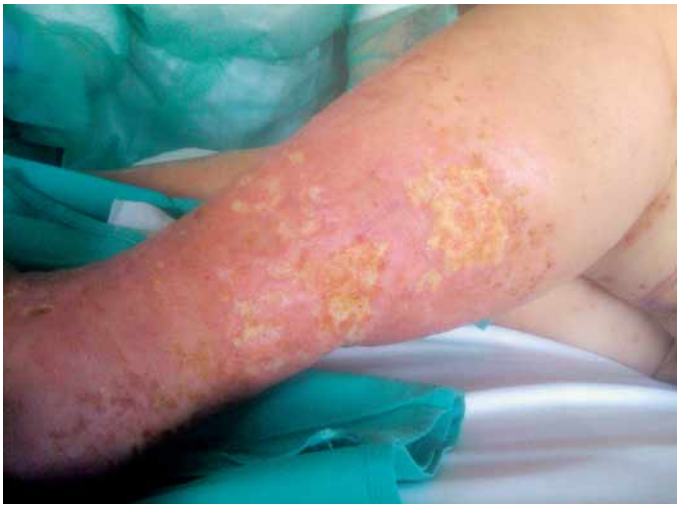

Fig. 2
Appearance after 16 days of sevoflurane applications, when it was considered clinically cured.

The progress of the left leg ulcer was also very favorable. The ulcer was markedly improved in appearance, showing a moderate reduction in area but an almost total resolution of its depth. As stated above, on the sixteenth day of sevoflurane applications, the left leg ulcer was considered closed (▶Fig. 2) and the sevoflurane treatment concluded.

The patient's clinical progress was very slow, however, owing to complications with the right leg ulcer, which was treated conventionally with silver sulfadiazine applications and dressings. This ulcer developed a MRSA superinfection. The patient was treated with intravenous vancomycin and developed a generalized, bullous exanthem diagnosed as vancomycin-induced linear IgA dermatosis. This necessitated her admission to ICU where she remained for three months due to subsequent complications – respiratory and urinary infections, renal and respiratory insufficiency, pulmonary bleeding due to vascular malformations in the bronchial and intercostal trunks – before being transferred back to the ward.

Discussion

In this clinical experience, we were able to confirm repeatedly that sevoflurane topically applied to an ulcer with refractory pain has a rapid and intense analgesic effect that lasts for hours. Moreover, the fact that this occurred in the context of the patient refusing other therapeutic options – the opioids because of the poisoning she suffered, the epidural because of her previous bad experience, and the cream because of the discomfort its application causes – makes it all the more worthy of further evaluation.

The classical thinking has been that the effect of inhalation anesthetic agents cannot be explained by a depression of peripheral receptors (8), which implies that, from a physiological standpoint, an analgesic effect such as that described in this case would not be possible.

> In our opinion, this apparent contradiction can be easily explained by considering the difference between administering sevoflurane by inhalation and administering it by local irrigation.

To date, the studies that have evaluated the possible peripheral analgesic effect of the halogenated anesthetic agents administered by inhalation have found no such analgesic effect, both in animal models (6) and healthy volunteers (9, 10). It is reasonable to suppose that, when a halogenated agent is administered by inhalation, the partial pressure it reaches in peripheral nociceptors may not be high enough to block transmission of a painful stimulus to any clinically significant degree, especially if it is administered at subanesthetic dosages (9, 10).

On the other hand, Fassoulaki et al. found a mild local analgesic effect of isoflurane solution applied on the forearm of healthy volunteers, what suggests that isoflurane may have an analgesic effect in the peripheral tissues (11). Even more, Chu et al. found that, after subcutaneous injection, several inhaled anesthetics (isoflurane, halothane, enflurane) produced a reversible, concentration-dependent cutaneous analgesic effect at the site of injection (12). Regarding our patient it is reasonable to suppose that, with direct irrigation of a wound, the nociceptors were exposed to a very high partial pressure of sevoflurane, high enough to block the transmission of painful stimuli.

In conclusion, we would like to emphasize that, in this case, the compassionate use of topical sevoflurane was critical to the management of an ulcer that was causing intractable pain. In our opinion, this calls for future studies and communications to evaluate the efficacy and safety of this innovative and promising use of sevoflurane as a topical anesthetic/analgesic.

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