

Topical Sevoflurane for pain management in chronic ulcers. A case report

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Case Report

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Background:

We present a case report and a literature review of the use of topical sevoflurane for pain management, liquid sevoflurane application is easy, simple, and innocuous, and it can run through all the surface of the ulcer. Leg ulceration may damage peripheral nerves by a variety of processes, such as ischemia, infection and inflammation and this may cause a disruption in the way the nerves respond to stimulus. Pain was described as the worst thing about having an ulcer. Systemic analgesia often causes severe systemic adverse effects, so the use of topical sevoflurane may improve quality of life, emergency admissions due to pain, infections or other ulcer-related complications.

Keywords: Sevoflurane, wound management, wound healing.

Pain is arguably the main problem associated with vascular ulcers because it deeply affects the patient's quality of life and leads to other long-term health problems, and its management requires the generalized use of topical and systemic analgesia. Some evidence suggests that direct instillation of sevoflurane into the vascular ulcer (i.e., topical irrigation over the affected area) has a rapid, intense, and durable anesthetic effect; however, the mechanism of action has not been fully elucidated, and larger studies are necessary^{2,6,12}.

Sevoflurane has been clinically used to induce and maintain anesthesia for decades, and its safety and clinical efficacy have been investigated amongst different patient profiles in many studies. Although the primary route of administration of sevoflurane is the inhalation of the volatile formulation for systemic anesthesia, there are recent studies that explore the local effects of sevoflurane as a topical agent in patients with chronic venous ulcers. Due to its efficacy in inducing local analgesia and promoting wound healing, topical sevoflurane can provide a combined solution to the unmet needs in safe pain management techniques and treatment agents for chronic venous ulcers.⁷

Case report

A 37-year-old female patient with a history of hyperthyroidism, she arrived at the emergency department with two leg ulcers which were very painful at a 10/10 intensity on the visual analog scale. Measuring 11 x 7 cm for the upper ulcer and 14 x 13

cm for the lower one. She underwent surgical debridement, biopsy, and culture, and started empiric antibiotic therapy. Negative pressure wound therapy was initiated. The patient had a complicated clinical course with no improvement in pain. We used opioid and pregabalin as treatment of the pain.

Negative pressure wound therapy was discontinued, and honey dressings were started without improvement of the pain.

We started topical sevoflurane for pain management at a dose of 1 ml per cm² of ulcer area, after the first application the pain diminished 8/10 on the visual analog scale. After a week we increased to up to 3 daily doses and we suspended the opioid, the pain was 4/10. After three weeks home care continued with alginate dressings for both ulcers, the alginate was changed weekly, and the pain disappeared. Five weeks after the onset of the condition, skin grafts were performed on the top ulcer, which fully healed four weeks after the graft. The bottom ulcer completely healed 8 weeks after being discharged.

The patient only reported itching at the time of sevoflurane application, which improved over time.

Discussion

Sevoflurane has been clinically used to induce and maintain anesthesia for decades, and its safety and clinical efficacy have been investigated amongst different patient profiles in many studies. Sevoflurane has low blood and tissue solubility and is metabolized for free fluoride and hexafluoroisopropanol.^{4,7} Volatile anesthetics have an impact on the cardiovascular

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Figure 1. Upper ulcer.

system, either through effects on the myocardium itself or by decreasing systemic vascular resistance. Although the primary route of administration of sevoflurane is the inhalation of the volatile formulation for systemic anesthesia, there are recent studies that explore the local effects of sevoflurane as a topical agent in patients with chronic venous ulcers.^{3,7} Leg ulceration may damage peripheral nerves by a variety of processes, such as ischemia, infection and inflammation and this may cause a disruption in the way the nerves respond to stimulus. This can lead to a neuropathic component to the pain where sensitized nerves produce an exaggerated response to touch; a small painful stimulus may result in extreme pain. Pain was described in both quantitative and qualitative studies as the worst thing about having an ulcer this restricted physical activities such as walking and was frequently associated with leg and ankle Oedema. Leg ulcer pain often occurred at night and prevented patients from getting a full night's sleep.^{6,8}

The assessment of pain is difficult because it is a multifaceted expression of affective, cognitive, physical, sensory, behavioral, social-cultural, and subjective responses. A 2012 Cochrane review that evaluated data from 8 randomized clinical trials involving a total of 813 patients showed an improvement in debridement pain with the use of a eutectic mixture of local anesthetic (lidocaine 2.5% and prilocaine 2.5%) or slow-release ibuprofen foam dressings, as compared with placebo use (although that review did not find enough evidence to assess the effects of those interventions on wound healing); this finding contrasted sharply with results of other studies suggesting that the degree of wound healing could be considered as a marker of treatment success on its own.²

In human trials, sevoflurane used topically was shown to increase responses to electrical stimuli; however, it has also been shown to attenuate mechanical stimuli. This may be explained similarly to fiber sensitivity to local anesthetics. Cutaneous C fiber nociceptors are not sensitized by mechanical stimulation, A-delta (Ad) fibers respond to mechanical stimuli only, and both electrical and mechanical



Figure 2. Lower ulcer.

stimulation sensitizes A beta (Ab) afferents at non-noxious levels. Ad fibers have much faster conduction velocities at 5 – 40 m/s compared to 0.5 – 2 m/s of C fibers with non-significant differences in fiber diameter. Ad fibers, therefore, may be preferentially inhibited by topical sevoflurane. However, at high concentrations, a full analgesic effect can be seen. Motor neuron response in isolated rat pup spinal cords to single, repetitive C fiber stimulation was completely abolished action potentials with 250 ug of sevoflurane, causing both analgesia and paralysis. Separately, pain can be caused by bacterial-derived growth factors directly influencing membrane receptors leading to pore assembly and calcium ion influx, causing nociceptive fiber activation and sensitization as a contributory mechanism to their survival.⁷

An experiment with rats explores cicatrization with the exposure of complete skin defects to oxygen and sevoflurane gas type. A delayed cicatrization is observed with a longer exposure time of sevoflurane. A diminished collagen type 1 synthesis, an absence of collagen fibre maturation, a larger acute phase inflammatory cells accumulation and a lower transforming growth factor- β 1 and basic fibroblastic growing factor expression were observed. They suggest that healing effects can occur because of a vasodilator effect improving microcirculation, increasing the intake of nutrients and oxygen and decreasing inflammatory agents. Sevoflurane may have a vasodilator effect by a direct inhibitor effect on the vascular smooth muscle independent of the endothelium.^{5, 9, 13}

Vascular endothelium plays an important role in the regulation of peripheral vascular tone *in vivo* by releasing various vasoactive substances, such as nitric oxide (NO) or endothelium-derived hyperpolarizing factor (EDHF). In isolated arterial preparations, sevoflurane inhibited both NO-mediated and EDHF-mediated endothelium-dependent vasorelaxation. NO

and EDHF signaling pathways both appear to be involved in the contractile response to norepinephrine in the presence of endothelium. As described previously, sevoflurane inhibits NO and EDHF-mediated vasorelaxations, suggesting its ability to inhibit both the NO and the EDHF pathways. Therefore, it may be hypothesized that sevoflurane enhances the contractile response to norepinephrine by inhibiting the NO and/or EDHF pathways.⁵

A bactericidal effect of isoflurane and sevoflurane has been reported against different pathogens when the microorganisms, in suspension or on solid media, were exposed to their vapor form. A liquid-liquid model was used with isoflurane and other molecules with good antibacterial results.¹

Inflammatory pain during infection has been thought to be triggered by the action of immune-derived proteins (e.g. cytokines and growth factors), lipids (e.g. prostaglandins), and other mediators like amines, potassium, and protons on receptors expressed by nociceptors. We found that bacterial-derived factors directly activated nociceptors and contributed to hyperalgesia *in vivo*.¹⁰

Therefore, we are cautious in attributing the healing property exclusively to a direct bactericidal effect of sevoflurane, but it may be an important factor.¹

Liquid sevoflurane application is easy, simple, and innocuous, and it can run through all the surface of the ulcer. A tolerance effect has not been found with subsequent sevoflurane applications. Topical sevoflurane significantly decreases the pain, inducing a better tolerated cleaning of the wound. Sevoflurane treatment consisted of applying 100% sevoflurane to the ulcer at a dose of 1 mL per cm² of ulcer area; this was done once daily during the first week and increased to up to 4 daily doses as needed (to maintain a VAS score of 2–3) for up to 90 days.² Several analgesic treatments can induce commonly severe adverse effects in old patients with higher morbidity and mortality. Sevoflurane may reduce health costs by decreasing the use of other pain drugs. Its secondary effects allow less medical attention and hospitalization, and there are fewer physical, psychiatric, familial, and social complications.¹¹

Conclusion

Topical sevoflurane is a good option for managing pain in patients with chronic ulcers, because has an intense, fast and long-lasting analgesic effect, its vasodilator effect could help the wound, the possible bactericidal effect, and its safe profile.

Conflicts of interests

There was no conflict of interest during the study, and it was not funded by any organization.

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References

1. Rueda-Martínez JL, Gerónimo-Pardo M, Martínez-Monsalve A, Martínez-Serrano M. Topical sevoflurane and healing of a post-operative surgical site superinfected by multi-drug-resistant *Pseudomonas aeruginosa* and susceptible *Staphylococcus aureus* in an immunocompromised patient. *Surg Infect (Larchmt)* [Internet]. 2014;15(6):843–6.
2. Dámaso Fernández-Ginés F, Cortiñas-Sáenz M, Mateo-Carrasco H, de Aranda AN-G, Navarro-Muñoz E, Rodríguez-Carmona R, et al. Efficacy and safety of topical sevoflurane in the treatment of chronic skin ulcers. *Am J Health Syst Pharm* [Internet]. 2017;74(9):e176–82.
3. Brioni JD, Varughese S, Ahmed R, Bein B. A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics. *J Anesth* [Internet]. 2017;31(5):764–78.
4. Kharasch EV, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition: I. Sevoflurane and metabolite pharmacokinetics. *Surv Anesthesiol* [Internet]. 1996;40(2):77.
5. Izumi K, Akata T, Takahashi S. The action of sevoflurane on vascular smooth muscle of isolated mesenteric resistance arteries (part 1): role of endothelium. *Anesthesiology* [Internet]. 2000;92(5):1426–40.
6. Herber OR, Schnepf W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. *Health Qual Life Outcomes* [Internet]. 2007;5(1):44.
7. Aranke M, Pham CT, Yilmaz M, Wang JK, Orhurhu V, An D, et al. Topical sevoflurane: A novel treatment for chronic pain caused by venous stasis ulcers. *Anesth Pain Med* [Internet]. 2021;11(1).
8. Briggs M, Nelson EA. Topical agents or dressings for pain in venous leg ulcers. En: Briggs M, editor. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
9. Imbernon-Moya A, Ortiz-de Frutos FJ, Sanjuan-Alvarez M, Portero-Sanchez I, Merinero-Palomares R, Alcazar V. Healing of chronic venous ulcer with topical sevoflurane. *Int Wound J* [Internet]. 2017;14(6):1323–6.
10. Chiu IM, Heesters BA, Ghasemlou N, Von Hehn CA, Zhao F, Tran J, et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* [Internet]. 2013;501(7465):52–7.
11. Imbernon-Moya A, Ortiz-de Frutos FJ, Sanjuan-Alvarez M, Portero-Sanchez I, Merinero-Palomares R, Alcazar V. Pain and analgesic drugs in chronic venous ulcers with topical sevoflurane use. *J Vasc Surg* [Internet]. 2018;68(3):830–5.
12. Salavastru CM, Nedelcu LE, Tiplica GS. Management of leg ulcers in patients with chronic venous insufficiency:

- the experience of a dermatology clinic in Bucharest, Romania. *Dermatol Ther.* 2012;25:304–13.
13. Lee H-J, Kwon J-Y, Shin S-W, Baek S-H, Choi K-U, Jeon Y-H, et al. Effects of sevoflurane on collagen production and growth factor expression in rats with an excision wound: Sevoflurane alters wound healing. *Acta Anaesthesiol Scand [Internet]*. 2010;54(7):885–93.

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