Rev Soc Esp Dolor
2018; 25(2): 106-111

DOI: 10.20986/resed.2017.3617/2017

Analgesic efficacy of topical sevoflurane on wounds

M. Gerónimo Pardo[1] and M. Cortiñas Sáenz[2]

[1]Especialista en Farmacología Clínica y en Anestesia y Reanimación. Servicio de Anestesiología, Reanimación y Terapéutica del Dolor. Complejo Hospitalario Universitario. Albacete.
[2]Especialista en Anestesiología y Reanimación. Unidad del Dolor. Servicio de Anestesiología, Reanimación y Terapéutica del Dolor. Hospital de Torrecárdenas. Almería. España

Gerónimo Pardo M, Cortiñas Sáenz M. Eficacia analgésica del sevoflurano tópico en heridas. Rev Soc Esp Dolor 2018;25(2):106-111.

ABSTRACT

Sevoflurane is a halogenated anesthetic derived from diethyl ether, which is presented as a volatile liquid. Administered by inhalation, it is widely used for inducing and maintaining general anesthesia, as it has a very good safety profile. In addition to its hypnotic action, various pre- clinical experiences show that sevoflurane and other halogenated ether derivatives bring about a significant analgesic/ anesthetic effect when administered in liquid form directly to the central nervous system, specifically to the spinal cord. However, it is classically thought they lack analgesic effect at peripheral level. However, clinical experiences in which sevoflurane had a major analgesic effect on painful wounds when it was irrigated in its liquid presentation on the bed of such wounds have been reported in recent years. This analgesic effect is characterized as taking place within a few minutes, as intense enough to allow sharp debridement of wounds, and as lasting for several hours. Concerning adverse effects, so far no case of systemic adverse events has been reported; only local adverse effects have been reported, the most frequent being mild, transitory itching. For the moment, clinical communications are limited to isolated clinical cases and case series of patients; obviously, relevant clinical trials are required to adequately establish the role of topical sevoflurane in the analgesic treatment of painful wounds. But while conducting these clinical trials, the off-label use of topical sevoflurane irrigated on the bed of painful wounds may be an alternative option for the analgesic treatment of wounds with pain refractory to usual treatments.

Key words: Sevoflurane, anesthetic inhalation, topical administration, pain, analgesics.

RESUMEN

El sevoflurano es un anestésico derivado halogenado del éter dietílico que se presenta como un líquido volátil. Es ampliamente utilizado por vía inhalatoria para la inducción y el mantenimiento de la anestesia general, pues su perfil de seguridad es muy bueno. Además de su acción hipnótica, diversas experiencias preclínicas muestran que el sevoflurano y otros derivados halogenados del éter producen un efecto analgésico/anestésico importante cuando son admi- nistrados en su formulación líquida directamente al sistema nervioso central, concretamente a la médula espinal, pero clásicamente se les considera carentes de efecto analgésico a nivel periférico. Sin embargo, en los últimos años se están comunicando experiencias clínicas en las que el sevoflurano produce un efecto analgésico importante sobre heridas dolo- rosas cuando es irrigado en su presentación líquida sobre el lecho de dichas heridas. Este efecto analgésico se caracteriza por instaurarse en escasos minutos, ser lo bastante intenso como para permitir el desbridamiento mecánico de las heridas, y extenderse por espacio de varias horas. Referido a efectos adversos, hasta ahora no ha sido comunicado ninguno a nivel sistémico, y el efecto local más frecuentemente referido por los pacientes es prurito leve y transitorio. Hasta ahora las comunicaciones clínicas se limitan a casos clínicos aislados y series de casos, y es obvio que se precisa la realización de los pertinentes ensayos

Received: 19-08-17.
Accepted: 31-08-17.

Correspondence: Manuel Gerónimo Pardo
sergepu@hotmail.com

clínicos para establecer adecuadamente su papel en el tratamiento analgésico de las heridas dolorosas. Pero mientras estos ensayos clínicos se realizan, el empleo fuera de indicación de sevoflurano irrigado tópicamente sobre el lecho de heridas dolorosas es una alternativa analgésica de rescate a tener en cuenta en aquellas heridas de dolor refractario a los tratamientos habituales.

Palabras clave: Sevoflurano, anestésicos por inhalación, administración tópica, dolor, analgésicos.

INTRODUCTION

Sevoflurane is a halogenated diethyl ether derivative. It is presented as a very volatile liquid, and it is widely administered by inhalation to subject patients to general anesthesia. After decades of use, it has proven to be an anesthetic with a very favorable benefit/risk balance (1), although its specific hypnotic action mechanism has not been fully elucidated (2).

Apart from its use as a hypnotic administered by inhalation, favorable clinical experiences have recently been reported relating to its topical use on wounds, whether for analgesic (3-11), antimicrobial (12-14) or healing (11) purposes. The objective of this review is to summarize the available information so far regarding topical use of sevoflurane focusing on its use as an anesthetic / analgesic on wounds.

PERIPHERAL ANALGESIC EFFECT OF TOPICAL SEVOFLURANE

Peripheral analgesic effect of halogenated anesthetetics

Classically, halogenated ether anesthetics, in general, and sevoflurane in particular, have been considered to produce an analgesic effect at a central level (15) but they lack an analgesic effect at peripheral level (16). Below, we briefly examine the tests in favor and against.

Pre-clinical experiences using halogenated ether derivatives

Several experiments exist in which healthy volunteers inhaled subanesthetic doses of halogenated anesthesia for short periods of time and were subjected to different painful cutaneous stimuli (17,18). None of these works found that the drugs studied produces a significant analgesic effect. It has been objectively determined when topically administered to healthy volunteers and in animal experimentation. Irrigation with isoflurane and sevoflurane of forearms dressed in gauze, covered with plastic and left to act for 30 minutes, produced a slight local analgesic effect measured with mechanical and electric stimulation tests (19,20). This application method has the disadvantage of being rather inconvenient, and the analgesic effect found was of low intensity, which hampered finding a clinical application. Seemingly, skin acted as a barrier for dispersing the anesthetic and interfered with the anesthetic effect, because in an in vivo study carried out on rats the subcutaneous injection of isoflurane and desflurane produced a dose-dependent local analgesic effect, similar to the one obtained in the same experiment with subcutaneous injection with the local anesthetics lidocaine and prilocaine (21). This last work led to the administration of halogenated drugs on wounds (22), because the loss of the existing cutaneous barrier in a wound means that administration by drug irrigation to the base of an ulcer is comparable to its subcutaneous injection.

Clinical experiences using ether and its halogenated derivatives

At the beginning of the 20th century, certain reports appeared in which diethyl ether was used topically for antimicrobial purposes in cavities as a single treatment for peritonitis (23) and arthritis (23), and also irrigated on infected wounds (23-25). None of these reports make any mention of ether's potential analgesic effect; quite the contrary, in some patients it caused irritation to the skin surrounding the wound (25).

From then on, the antimicrobial effect of ether and of its halogenated derivatives has been studied in vivo in experimentation with animals (26) and in vitro (27-29), but the clinical reports focused on their potential antivirus role in treating labial and genital herpes (30,31). The application of swabs soaked in ether to herpes simplex wounds caused a burning pain that was occasionally defined as worse than the pain of the disease, but it was followed by a local analgesic effect (30,31).

After some years without reports of the antimicrobial employment of ether or its halogenated derivatives, recent reports have described the antimicrobial use of sevoflurane in several patients

affected by complicated infected wounds (12-14). As mentioned above, the object of this review is not employment on wounds for an antimicrobial effect, but for analgesic/anesthetic purposes.

Clinical experiences in the topical use of sevoflurane as an analgesic

The first clinical experience in the satisfactory use of sevoflurane as a topical analgesic corresponds to the year 2011. It was a patient affected by a venous ulcer with uncontrollable pain. The patient rejected the use of an epidural catheter owing to a previous negative experience, the use of opioids due to having previously undergone a near-fatal intoxication with these drugs, and EMLA cream due to the pain associated with its application; in this context, the compassionate use of sevoflurane rinsing immediately controlled the pain daily and for a period of 10-12 hours, and were very well tolerated by the patient (whose mood spirit improved considerably), and did not interfere with the healing of the wound, which closed in 16 days. As the only adverse effect, the patient suffered pruritus in the area of healthy skin surrounding the wound, which could be controlled by preventing the sevoflurane from going beyond the edges of the wound; the patient's satisfaction level was very high (3).

As from then, more clinical experiences have been reported regarding the analgesic effect of topical sevoflurane, both in isolated clinical cases (4-6,8,10) and in small case series (7,9,11); the analgesic effect has also been objectively determined in two patients where it was used for antimicrobial purposes (12,13); in total, more than 1,500 applications of sevoflurane have been reported on almost 150 patients (Table I).

The common conclusion regarding analgesic efficacy is that the application of liquid sevoflurane is painless by itself, and the analgesic effect appears in a few minutes, is so intense that it frequently allows mechanical debridement of the wound, and lasts for a period of several hours. Furthermore, there are reports regarding patients treated with sevoflurane daily on an outpatient basis for months and even years (9-11) and so far the is no objective determination that it produces tolerance; each application produces the same effect as the first time (9-11).

SAFETY OF TOPICAL SEVOFLURANE

Systemic effects

Systemic effects for the patient

Topical rinsing of wounds with sevoflurane has proven to be very safe for patients, because none of the applications mentioned above reported systemic adverse effect (3-14). This may be because most of these applications were carried out in small doses (up to 20 ml) and on chronic wounds with vascular etiology, where blood perfusion is deteriorated, so it is feasible to suppose that absorption into the venous circulation system takes place slowly and the partial blood pressures of sevoflurane would be low.

But additionally, as it is a volatile molecule, it is to be

TABLE I

CHRONOLOGICAL SUMMARY OF PATIENTS TREATED WITH TOPICAL SEVOFLURANE REPORTED IN THE LITERATURE

Author and year (reference)	*Number of subjects*	*Accumulated days of treatment*
Gerónimo Pardo, 2011 (3)	1	16
Martínez Monsalve, 2011 (4)	1	3
Martínez Monsalve, 2013 (5)	9	76
Rueda Martínez, 2014 (11)	1	4
Imbernón, 2016 (6)	1	21
Ferrara, 2016 (12)	1	15
Villarroel, 2016 (7)	89	89
Fernández Ginés, 2017 (8)	1	35
Fernández Ginés, 2017 (9)	11	72.0 ± 18.5
Amores Valenciano, 2017 (10)	1	≈ 365
Imbernón-Moya, 2017 (13)	3	45
Imbernón-Moya, 2017 (14)	30	360
TOTAL	**149**	**≈ 1,850**

expected that as part of the quantity of circulatin sevoflurane diffused to the alveolus passes through the alveolar capillaries and is exhaled in what could be called the "first pulmonary stage", which would constitute an additional safety mechanism when it is used topically (32); this consideration has not been sufficiently studied, but there are clinical experiences with ether that support it. In fact, systemic effects have only been reported with the non-inhalation of ether when it was applied or in high doses or in body cavities, or both. The most paradigmatic example is rectal etherization, consisting of administering about 30 ml of ether rectally to achieve surgical hypnosis (33) or to treat childbirth pains (34), so the hypnosis cannot be considered an adverse effect, but intended; used this way, the scent of ether was noticable both on the patient's breath and in the room, which demonstrates pulmonary elimination (33). As regards undesired effects, it has been described that the administration of more than 90 ml ether in the peritoneum as antiseptic treatment for peritonitis caused hypmosis for hours in some patients, although all recovered without secondary effects (23). No undesired systemic effects have been reported in the intraperitoneal administration of less than 90 ml (23), in the intra-articular injection of small amounts of ether to treat septic arthritis (23), in rinsing with abundant amounts of ether for infected wounds (23-25), nor when the wounds were subjected to an ether bath of for a period of 30 minutes (25).

Considering that the anesthetic effect of ether is very similar to that of sevoflurane, because both present an approximate MAC value of 2 (1.35), it is reasonable to suppose that the risk of systemic effects appearing in the specific context of administering sevoflurane on complicated wounds is minimal in doses lower than 50 ml.

Local effects

Local effects for the patient

Unlike systemic effects, there have been reports of undesired local effects with the administration of sevoflurane, specifically a feeling of pruritus; this effect is quite frequent, especially on perilesional skin, but it is usually well tolerated and does not lead patients to reject the treatment (3,6-9,11). As mentioned above, this irritation has also been described with ether applications (25,30,31).

Local effects for the wound

It is clear that the benefit/risk balance would be unfavorable if the analgesic effect included a deterioration of the wound conditions due to the administration of sevoflurane, so it is worth commenting on the potential local toxicity of sevoflurane. But as this aspect has not been formally studied, we must again resort to indirect tests.

In a preclinical study carried out on rats, it was found was that the intra-peritoneal injection of isoflurane, a halogenated derivative of ether, and of halothane, a halogenated alcohol, caused fibrosis in all retroperitoneal organs of the rats studied (36). Conversely, sevoflurane did not cause any alteration in such organs, even applied at lethal dose (36). This difference in results may be due to the absence of chlorine in the sevoflurane molecule and its presence in those of isoflurane and halothane, although this aspect has not been studied.

Disregarding speculations, what is clear is that at clinical level the clinical results obtained with the administration of ether and sevoflurane have been very favorable and in general wounds, instead of worsening, evolved to healing, even when superinfected (3-14, 23-25), so that so far the benefit/risk balance is favorable.

FUTURE QUESTIONS

There is a great deal to clarify. This field is so new that almost none of its aspects have been formally studied. Until now all the accrued experience is based on isolated clinical cases and on small case series. Aspects as important as whether it may be useful in all kinds of chronic painful wounds (gangrenous pyodermas, Martorell's ulcers, etc.) or whether it has any role in the analgesia of the acute wounds, apart from its potential role as an antiseptic in infected wounds,-apart from the most suitable type of formulation (cream, gel, microspheres [37]) remain to be studied for its potential use outside a hospital environment (8,9) in treating wounds and other chronic painful processes, frequency of application, maximum dose, route to minimize environmental contamination; the possible use of other halogenated ether derivatives, the long-term possibility of toxic effects, etc. And obviously, it is essential to carry out controlled clinical trials to establish their topical analgesic role in comparison with other topical alternatives, especially EMLA cream (38).

CONCLUSIONS

In view of the existing literature, rinsing of the painful wound bed with sevoflurane produced a rapid, intense and lasting analgesic effect. It is easily administered and painless by itself, and has a very favorable secondary effect profile. Accordingly, and while the relevant clinical trials need to be carried out, the off-label topical use of sevoflurane may be a valid rescue option in situations of painful wounds that are difficult to manage.

CONFLICTS OF INTEREST

Dr. Cortiñas Sáenz declares he has no conflict of interest. Dr. Gerónimo Pardo declares he has received fees as conference speaker at the companies Abbott and Abvvie, and acts as external consultant for the company Vapogenix.

REFERENCES

1. Brioni JD, Varughese S, Ahmed R, Bein B. A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics. J Anesth 2017;31(5):764-78. DOI: 10.1007/s00540-017-2375-6.
2. Solt K, Forman SA. Correlating the clinical actions and molecular mechanisms of general anesthetics. Curr Opin Anaesthesiol 2007;20(4):300-6.
3. Gerónimo Pardo M, Martínez Monsalve A, Martínez Serrano M. Analgesic effect of topical sevoflurane on venous leg ulcer with intractable pain. Phlebologie 2011;40:95-7.
4. Martínez Monsalve A, Gerónimo Pardo M. Sevoflurano como analgésico local en herida isquémica de paciente cardiópata con insuficiencia respiratoria secundaria a morfina. Heridas y Cicatrización 2011;2(6):46-9.
5. Martínez-Monsalve A, Gerónimo-Pardo A. Efecto analgésico de sevoflurano aplicado tópicamente sobre úlceras varicosas dolorosas en pacientes ambulatorios. Heridas y Cicatrización 2013;1:16-9.
6. Imbernón A, Blázquez C, Puebla A, Churruca M, Lobato A, Martínez M, Aguilar A, Gallego MA. Chronic venous ulcer treatment with topical sevoflurane. Int Wound J 2016;13(5):1060-2. DOI: 10.1111/iwj.12474.
7. Villarroel A. Efecto del sevoflurano tópico para analgesia en lesiones ulcerativas dolorosas de pacientes diabéticos (trabajo de postgrado). Universidad de Oriente, Núcleo de Sucre, Venezuela; 2016.
8. Fernández Ginés FD, Cortiñas Sáenz M, Fernández Sánchez C, Morales Molina JA. Sevoflurano tópico: una nueva opción terapéutica en las úlceras cutáneas. MEDIPAL 2017;24:104-8. DOI: 10.1016/j.medipa.2015.03.003.
9. Fernández-Ginés FD, Cortiñas-Sáenz M, Mateo-Carrasco H, de Aranda AN, 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 2017;74(9):e176-82. DOI: 10.2146/ajhp151008.
10. Amores Valenciano P, Navarro Carrillo A, Romero Cebrián MA, Gerónimo Pardo M. Sevoflurano tópico como terapia de rescate de dolor refractario en úlceras venosas crónicas. Emergencias 2017; en prensa.
11. Imbernon-Moya A, Ortiz-de Frutos FJ, Sanjuan-Álvarez M, Portero-Sánchez I, Merinero-Palomares R, Alcazar V. Topical sevoflurane for chronic venous ulcers infected by multi-drug-resistant organism. Int Wound J 2017;14(6):1323-6. DOI: 10.1111/iwj.12806.
12. Rueda-Martínez JL, Gerónimo-Pardo M, Martínez-Monsalve A, Martínez-Serrano M. Topical sevoflurane and healing of a postoperative surgical site superinfected by multi-drug-resistant Pseudomonas aeruginosa and sensitive Staphylococcus aureus in an immunocompromised patient. Surg Infect (Larchmt) 2014;15(6):843-6. DOI: 10.1089/sur.2013.079.
13. Ferrara P, Domingo-Chiva E, Selva-Sevilla C, Campos-García J, Gerónimo-Pardo M. Irrigation with liquid sevoflurane and healing of a postoperative, recurrent epidural infection: a potential cost-saving alternative. World Neurosurg 2016;90:702.e1-5. DOI: 10.1016/j.wneu.2016.02.079.
14. Imbernón-Moya A, Ortiz-de-Frutos FJ, Sanjuan-Álvarez M, Portero-Sánchez I, Merinero-Palomares R, Alzacar V. Topical sevoflurane for chronic venous ulcers infected by multidrug-resistant organisms. Int Wound J 2017;14(6):1388-90. DOI: 10.1111/iwj.12794.
15. García Fernández J, Parodi E, García P, Matute E, Gómez de Segura IA, Cediel R, Gilsanz F. Clinical actions of subarachnoid sevoflurane administration in vivo: a study in dogs. Br J Anaesth 2005;95(4):530-4.
16. Koblin DD. Mechanism of action. In: Miller RD, ed. Anesthesia, 5th ed. Filadelfia, USA: Churchill Livingstone; 2000. p. 48-73.
17. Tomi K, Mashimo T, Tashiro C, Yagi M, Pak M, Nishimura S, et al. Alterations in pain threshold and psychomotor response associated with subanesthetic concentrations of inhalation anaesthetics in humans. Br J Anaesth 1993;70(6):684-6.
18. Petersen-Felix S, Arendt-Nielsen L, Bak P, Roth D, Fischer M, Bjerring P, et al. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by experimentally induced pain. Br J Anaesth 1995;75(1):55-60.
19. Fassoulaki A, Sarantopoulos C, Karabinis G, Derveniotis C. Skin application of isoflurane attenuates the responses to a mechanical and an electrical stimulation. Can J Anesth 1998;45(12):1151-5.
20. Fassoulaki A, Skouteri I, Siafaka I, Sarantopoulos C. Local application of volatile anesthetics attenuates the response to a mechanical stimulus in humans. Can J Anesth 2005;52(9):951-7.
21. Chu CC, Wu SZ, Su WL, Shieh JP, Kao CH, Ho ST, et al. Subcutaneous injection of inhaled anesthetics produces cutaneous analgesia. Can J Anesth 2008;55(5):290-4. DOI: 10.1007/BF03017206.
22. Fernández Ginés FD, Cortiñas Sáenz M, Navajas-Gómez de Aranda A. Topical sevoflurane for skin ulcers: a new option in palliative care. Saarbrücken: LAP Lambert Academic Publishing; 2016.
23. Waterhouse HF. The employment of ether in surgical therapeusis, with special reference to its use in septic peritonitis, pyogenic arthritis, and gunshot wounds. Br Med J 1915;1(2823):233-7.
24. Livingstone J. Ether as a disinfectant. Br Med J

1915;1(2826):398.
25. Distaso A, Bowen TR. Auto-disinfection of wounds by the use of ether solution. Br Med J 1917;1(2930):259-61.
26. Topley WWC. The action of ether on certain micro-organisms. Br Med J 1915;1(2823):237-8.
27. Kristiansen JE, Amaral L. The potential management of resistant infections with non-antibiotics. J Antimicrob Che- mother 1997;40(3):319-27.
28. Bàtai I, Kerény M, Tekeres M. The impact of drugs used in anaesthesia on bacteria. Eur J Anaesthesiol 1999;16(7):425-40.
29. Martínez-Serrano M, Gerónimo-Pardo M, Martínez-Monsalve A, Crespo-Sánchez MD. Bactericidal effect of sevoflurane and isoflurane against multidrug resistant bacteria. Rev Esp Quimioter 2017;30(2):84-9.
30. Farrell RG, Nesland RS. Topical ethyl ether therapy of herpes simplex lesions. JACEP 1977;6(8):372-3.
31. Corey L, Reeves WC, Chiang WT, Vontver LA, Remington M, Winter C, et al. Ineffectiveness of topical ether for the treatment of genital herpes simplex virus infection. N Eng J Med 1978;299(5):237-9.
32. Gerónimo Pardo M, Martínez Serrano M, Martínez Monsalve A, Rueda Martínez JL. Usos alternativos del sevoflurano: efecto analgésico tópico. Rev electron AnestesiaR 2012;4(4):181.
33. Sutton WS. Anaesthesia by colonic absorption of ether. Ann Surg 1910;51(4):457-79.
34. Stevens WJ. Rectal ether analgesia in childbirth. Can Med Assoc J 1932;26(2):178-81.
35. Saidman LJ, Eger II EI, Munson ES, Babad AB, Muallem M. Minimum alveolar concentrations of methoxyflura ne, halothane, ether and cyclopropane in man: correlation with theories of anestesia. Anesthesiology 1967;28(6):994-1002.
36. Levine S, Saltzman A. Fluorinated anesthetics differ in toxic effects on peritoneum and subjacent tissues. J Appl Toxicol 1998;18(1):79-80.
37. Fernández-Ginés FD, Martínez Escobar S, Rodríguez Cuadros TB. A new controlled release system for pain & healing of cutaneous ulcers. Saarbrücken: LAP Lambert Academic Publishing; 2017.
38. Briggs M, Nelson EA, Martyn-St James M. Topical agents or dressings for pain in venous leg ulcers. Cochrane Databa- se Syst Rev 2010;(4):CD001177. DOI: 10.1002/14651858. CD001177.pub2

- 1. .