

REVISIÓN

Topical sevoflurane and early and sequential punch grafting in arteriolosclerotic leg ulcers: a case series

Sevoflurano tópico e injertos en sello precoces y secuenciales en úlceras arterioloscleróticas: una serie de casos

ABSTRACT:

Introduction: Leg ulcers secondary to arteriolosclerosis may be included in the clinic- histopathological spectrum of Martorell hypertensive ischemic ulcer. Consequently, they could be considered to benefit from the same treatment. Early punch grafting is an effective technique for pain control and healing promotion in Martorell ulcer. Moreover, the off-label use of topical sevoflurane has been described to be beneficial both in pain control and wound epithelization. We present the first case series of arteriolosclerotic ulcers managed with combined use of topical sevoflurane and early and sequential punch grafting.

Patients and methods: Patients with arteriolosclerotic ulcers treated with topical sevoflurane and punch grafting and adapted compression therapy at Hospital Virgen de la Torre from July 2021 to January 2022 were included in a case series. The primary endpoint was time to complete epithelialization and several secondary variables were registered. A Likert scale was used to measure pain. The presentation of the results is descriptive.

Results: Five patients were recruited, all of them female sex, aged between 67 and 84 years. They associated comorbidities such as hypertension,

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diabetes mellitus and chronic venous insufficiency, with an evolution time from 2 weeks and 8 months. Hospital admission was performed in all cases and all of them received at least two treatment sessions with punch grafting. The time interval until complete epithelialisation of the ulcers ranged from 6 weeks to 6 months. When asked, all patients reported that pain had decreased significantly since the grafting were placed, even the next day.

Discussion: The results of our study show how the combination of irrigated sevoflurane, compression therapy and stamp grafts is an effective combination to reduce pain and promote epithelialization of arteriosclerosis ulcers. This treatment, which can be performed on an outpatient basis, is well tolerated by patients and can be repeated several times if necessary.

RESUMEN:

Introducción: Las úlceras por arteriosclerosis pueden incluirse en el espectro clínico-histopatológico de la úlcera isquémica hipertensiva de Martorell. En consecuencia, podría considerarse que se benefician del mismo tratamiento. La realización precoz de injertos en sello es una técnica eficaz para el control del dolor y la promoción de la cicatrización en la úlcera de Martorell. Además, se ha descrito que el uso fuera de etiqueta de sevoflurano tópico es beneficioso tanto en el control del dolor como en la epitelización de heridas. Presentamos la primera serie de casos de úlceras por arteriosclerosis tratadas con sevoflurano tópico en combinación con injertos en sello precoces y secuenciales.

Pacientes y métodos: Se incluyeron en una serie de casos de pacientes con úlceras arterioscleróticas tratadas con sevoflurano tópico, injertos en sello y terapia compresiva adaptada en el Hospital Virgen de la Torre de Madrid, desde julio de 2021 hasta enero de 2022. Se registraron diversas variables, siendo la variable principal el tiempo hasta alcanzar la epitelización de la herida. Se utilizó una escala de Likert para medir el dolor. La presentación de los resultados es descriptiva.

Resultados: Se reclutaron 5 pacientes, todos de sexo femenino, con edades comprendidas entre los 67 y los 84 años. Asociaron comorbilidades como hipertensión, diabetes mellitus e insuficiencia venosa crónica, con un tiempo de evolución de entre 2 semanas y 8 meses. En todos los casos se realizó ingreso hospitalario y todos recibieron al menos dos sesiones de injertos en sello. El tiempo hasta la epitelización completa de las úlceras osciló entre 6 semanas y 6 meses. Al ser preguntados, todos los pacientes refirieron que el dolor había disminuido notablemente desde que se colocaron los injertos, incluso al día siguiente.

Conclusión: Los resultados de nuestro estudio muestran cómo la combinación de sevoflurano irrigado, terapia compresiva e injertos en sello es una combinación eficaz para reducir el dolor y promover la epitelización de las úlceras por arteriosclerosis. Este tratamiento, que puede realizarse de forma ambulatoria, es bien tolerado por los pacientes y puede repetirse varias veces si es necesario.

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Palabras clave: *Sevoflurano tópico, injertos en sello, úlcera arteriosclerótica de la pierna, arteriosclerosis, úlcera de Martorell, HYTILU, úlcera isquémica hipertensiva de la pierna, dolor.*

Introduction

Large and painful wounds secondary to arteriosclerosis are a frequent reason for consultation. These wounds progressively acquire a purplish or blackish colour and, in a few days, become extensive, deep and very painful wounds. In addition to age, these patients often have comorbidities such as hypertension or diabetes.

This clinical description is similar to Martorell hypertensive ischemic ulcer. In fact, some of these arteriosclerotic ulcers, which are frequently post-traumatic lesions, may be considered Martorell ulcers, as they have the characteristics traditionally associated with this entity (typical lateral and posterior location on the leg, bilaterality, hypertension or diabetes mellitus). The rest of the wounds that do not meet the criteria included in the traditional Martorell definition, could be called “ulcers due to age-associated arteriopathy”. Skin biopsy does not help to differentiate them because, histopathologically, both types of wounds present occlusive subcutaneous arteriosclerosis. The results of a recent retrospective study comparing leg biopsy findings of patients with and without Martorell ulcer conclude that arteriosclerosis present in both groups is associated with age (1).

Punch grafting is a traditional method to obtain thin split-thickness skin grafts containing epidermis and papillary dermis. Grafts are obtained under a local anaesthetic with a punch, curette or surgical blade and are placed directly on the wound bed. The donor site is normally the thigh, which heals by secondary intention. The procedure can be performed in an outpatient basis (2,3).

Early punch grafting is considered the first line treatment for Martorell leg ulcers in France, mainly for its benefit in pain reduction and limitation of wound progression (4). Even if the wound bed does not present with perfect conditions for grafting, punch grafts that do not succeed to adhere do release growth factors and cells that promote wound epithelialization and reduce pain (2,5,6). In these cases, we have to perform several sessions of punch grafting to obtain complete epithelialization, something very well accepted by the patient (2,6).

Several experts support the interest of this technique in this type of wounds (2,4-7).

Regarding new analgesic strategies, more and more evidence is being published by Spanish authors regarding efficacy of sevoflurane (8-10). Sevoflurane is an inhalation anaesthetic agent, of the group of halogenated ethers, for use in induction and maintenance of general anesthesia. It is a colourless volatile liquid, packaged in 250 ml bottles, which is vaporised for use as an anaesthetic gas. It can therefore be used off-label in its liquid form, as a local anaesthetic, applied by irrigation to painful wounds. Although studies published in the literature are mostly isolated cases or short series, the results are promising. The benefit of topical sevoflurane seems not to be limited to its analgesic effect. It has been proposed that it can produce a healing acceleration due to its vasodilator effect and improve the response to punch grafting (7).

However, thus far, no case series have been published regarding the combination of topical sevoflurane and early and sequential punch grafting in arteriosclerotic ulcers.

We report a series of leg ulcers secondary to arteriosclerosis successfully managed with topical sevoflurane and sequential punch grafting.

Patients and method

Patients with arteriosclerotic ulcers treated with topical sevoflurane and punch grafting and adapted compression therapy at Hospital Virgen de la Torre from July 2021 to January 2022 were included in a case series. The primary endpoint was time to complete epithelialization. Several variables were registered including sex, age and comorbidities, as well as pain reduction, wound characteristics, number of dressing changes and grafts to complete wound epithelialisation, and need for hospital admission. A Likert scale (verbal numeric pain scale) was used to measure pain, as the analogue visual scale (VAS) for pain is sometimes not understood by patients. The presentation of the results is descriptive.

Results

During the aforementioned period, 5 patients (n = 5) were recruited, all of them female sex, aged between 67 and 84 years.

Ulcers due to arteriosclerosis, which are very painful, are increasingly frequent due to the aging of the population

They associated comorbidities such hypertension, diabetes and chronic venous insufficiency. The time interval of evolution of the ulcers was from 2 weeks to 8 months. Wound extension was widely variable, with a range up to 17 cm in diameter the largest ulcer included. In two of the patients, a skin biopsy of the wound edge was performed. In all cases, hospital admission was carried out for better compliance with absolute bed rest, receiving thromboprophylactic treatment with low molecular weight heparin. Dressing changes were spaced out as much as possible, taking place every 5-7 days. All patients received at least two treatment sessions with punch grafting. The time interval until complete epithelialisation of the ulcers ranged from 6 weeks to 6 months. No direct relationship between the time of evolution of the wound and the time until complete epithelialisation was observed. The variables studied are collected in Table I.

All patients were asked by means of a verbal scale how much pain they had from 1 to 10 in the first dressing change. Although it was also difficult to get them to answer a specific number, they all reported that the pain had decreased markedly since the grafting were placed, even the next day.

The patient in case 1 presented extremely painful multiple ulcers on the lower limbs, associated to phlebolinfedema (Figure 1). His right leg also had exposure of the Achilles tendon (Figure 2.C). These were the ulcers that took the longest to epithelialise, with a total of 6 months, requiring up to three punch graft sessions (Figures 2 and 3). The patient required the implantation of a neurostimulator for adjuvant pain control (Figure 4).

Case 2 was an 84-year-old woman who, due to a chronic heart failure decompensation, presented very painful necrotic plaques associated to edema on a lower left limb (Figure 5.A). Scares were debrided but the size of the lesions progressively increased (Figure 5.B and C). This patient was treated with daily irrigations with sevoflurane and two sessions of sequential punch grafting, presenting complete epithelialisation in two weeks (Figure 5.D).

The woman in case 3 had extensive ulcers on both lower limbs, associated with pain and phlebolympheidema (Figure 6.A and B). After receiving irrigations with topical sevoflurane and three sessions of punch grafting (Figure 6.C and D), epithelialisation was complete in 3 months (Figure 7).

Table I. Descriptive analysis of the features of the patients included in the series.

| | Age | Gender | Comorbidities | Months of evolution | Biopsy | Number of grafting sessions | Time to complete epithelialization |
|---------------|-----|--------|-------------------|---------------------|--------|-----------------------------|------------------------------------|
| Case 1 | 67 | Male | Hypertension CVI | 3 | Yes | 3 | 6 months |
| Case 2 | 84 | Female | Hypertension DM 2 | 2 | No | 2 | 3 months |
| Case 3 | 81 | Female | Hypertension CVI | 3 | Yes | 3 | 3 months |
| Case 4 | 83 | Female | Hypertension CVI | 8 | No | 2 | 6 weeks |
| Case 5 | 83 | Female | Hypertension DM 2 | 2 | No | 2 | 2 months |

Case 4 shows an 83-year-old woman who presented with a very painful ulcer that had lasted 8 months (the longest evolution time) (Figure 8.A). In the following weeks, the wound increased in size despite receiving a first session of punch grafting, but thanks to the combination with topical sevoflurane irrigations, the pain was controlled (Figure 8.B and C). The second grafting session was performed on an optimal wound bed, achieving complete epithelialisation in 6 weeks (Figure 8.D).

Finally, case 5 was an 83-year-old woman who presented an ulcer with irregular borders, necrosis, and bright erythema at its borders (Figure 9.A). After combined treatment with topical anesthetic and two punch graft sessions (Figure 9.B and C), epithelialisation was complete at two months (Figure 9.D).

Discussion

The results of our study show how the combination of irrigated sevoflurane, compression therapy and punch grafting are an effective combination to reduce pain and promote epithelialization of arteriolosclerosis ulcers.

Although Martorell ulcer is becoming increasingly known, little is said about the concept of arteriolosclerosis ulcers.

Available evidence suggests the first described cases of the Martorell ulcer in patients with poorly controlled hypertension corresponded to the extreme with greater clinical (necrosis, pain, and extension) and histological (arteriolosclerosis with greater hypertrophy of the wall secondary to poorly controlled hyperten-

There is no consensus on the treatment of choice for these lesions



Figure 1. Multiple ulcers on the lower limbs associated to phlebolinfedema.



Figure 2. Coverage of the ulcers with punch grafting. In C exposure of the Achilles tendon can be seen.



Figure 3. Complete epithelialisation.



Figure 4. Implantation of a neurostimulator for adjuvant pain control and compression bandage.



Figure 5. A: necrotic plaques associated to edema on a lower left limb. B and C: wound beds with granulation tissue. D: complete epithelialisation.

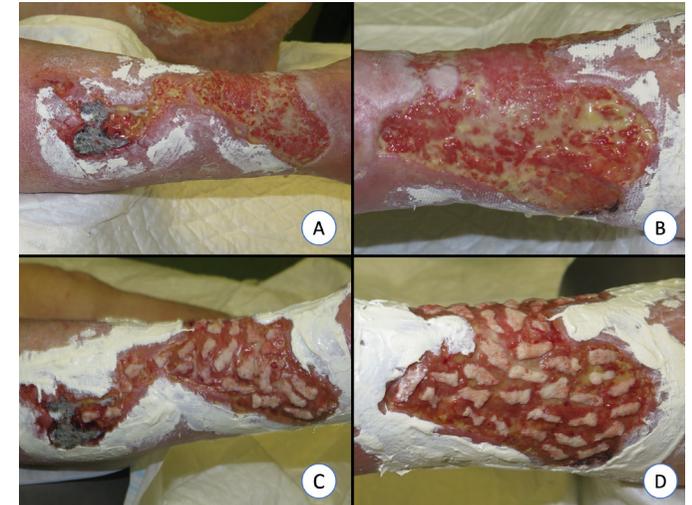


Figure 6. Anterolateral aspect of both legs, right (A) and left (B) associated with phlebolympheoedema. C and D: coverage with punch grafting.



Figure 7. Clinical evolution of the grafted ulcers, right (A) and left (B). C: complete epithelialisation.



Figure 8. A: six-months evolution ulcer. B: clinical evolution of the lesion. C: second grafting session performed on an optimal wound bed. D: complete epithelialisation.

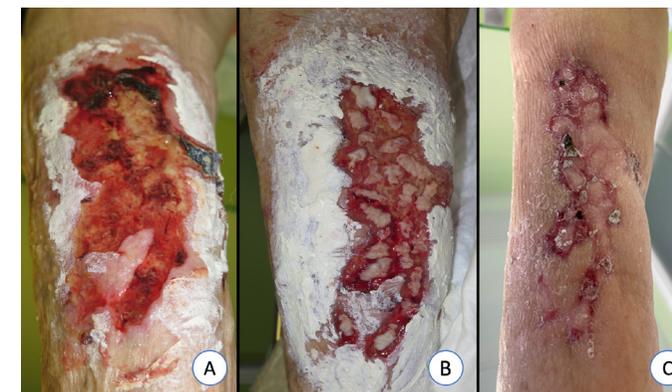


Figure 9. A: typical clinical presentation of arteriosclerosis ulcer. B: first session of punch grafting. C: complete epithelialisation.

sion) expressivity on the spectrum of “arteriopathy ulcers in the context of age, hypertension, and/or diabetes” (1).

With fewer and fewer deaths from major cardiovascular events, we are more frequently encountering minor cardiovascular events, such as arteriosclerosis ulcers. In fact, with the increased control of diabetes and hypertension, the clinical and histological presentation of arteriosclerosis ulcers in most cases is not as striking as in the early descriptions of Martorell ulcer in the literature.

The diagnosis of arteriosclerosis ulcers is clinical. They are leg ulcers with palpable distal pulses, very painful, with signs of necrosis, erythematous-violaceous borders, which may progress rapidly. A biopsy will only be performed to rule out other differential diagnoses, such as vasculitis or pyoderma gangrenosum, since arteriosclerosis can be found in the legs of any elderly or hypertensive person, it is not specific to patients with wounds (1).

Regarding treatment, ulcers in this spectrum could benefit from a similar therapeutic approach, which would stop the pathological cycle of necrosis-inflammation in these wounds (7,11).

In order to stop the pathological cycle of necrosis-inflammation, an anti-inflammatory and neo-angiogenic strategy is

ideal, so that tissue destruction is stopped and more oxygen may be provided to the wound.

For this purpose, in our clinical practice we use a combination of punch grafting, sevoflurane and compression therapy.

The angiogenic effect of early skin grafts counteracts the ischemic and pro-inflammatory environment in these wound beds, which is an essential promoter of wound healing and a constraining factor for skin necrosis (6).

As we have shown in our cases, even if the wound bed does not present with perfect conditions for grafting, punch grafts unsuccessful in adhering still release growth factors and cells that promote wound epithelialization and reduce pain, even though the exact mechanism of pain reduction is not well-known (6). Local pressure and immobilization during the first 4 to 5 days after the procedure are essential for graft taking. The first dressing change should take place 5 to 7 days after the surgical procedure. During subsequent dressing changes, which should be spaced as far apart as possible, it is essential to avoid excessive cleansing in order to not alter the pro-healing environment in the wound (6).

As in any leg ulcer, if no contraindication exists, compression therapy should be used to reduce inflammation and promote

healing (12). In addition, most patients in our series had edema associated with chronic venous insufficiency or congestive heart failure, making compressive therapy very beneficial.

It is important to emphasize that, as in one of these cases, ulcers due to arteriopathy can be triggered after rapid onset of edema due to heart failure. This is due to the fact that edema increases the space between the skin and the damaged arterioles, which can decrease perfusion, leading to ischemia and necrosis.

Even though we did not use them in our study, Negative Pressure Wound Therapy devices might be used to improve wound bed conditions before punch grafting, but also on the grafts to promote graft taking (13).

The ideal situation is to graft optimal beds with red granulation tissue. However, the patients who are older and with multiple comorbidities usually have associated pain and anticipatory anxiety for dressing changes (6,7). Although clinicians try to improve wound bed tissue as much as possible, it is not always easy to achieve optimal conditions for graft coverage, as seen in this series. Our experience shows that despite devitalized tissue in the bed and the absence of complete graft taking, the wound benefits from this coverage (6). Moreover, the present authors agree with the literature that invasive surgical debridement in these lesions may worsen the necrosis-inflammation cycle (5). Punch grafts behave like independent micro-islands—those that do not take should not affect the rest; they also are beneficial because they can release cells and growth factors for healing (6,7). In addition, the analgesic action of these grafts must be underlined, which, as observed in the authors' clinical practices, is independent of the percentage of graft taking. Repeated punch grafting sessions are well-tolerated by patients, due to its minimally invasive procedure, with a common rapid reepithelialization of the donor site (4-7).

An essential factor to promote graft attachment is absolute rest, with the legs elevated. Therefore, all our patients required hospital admission, since they had no possibility of family care at home.

In the present case series, before every punch grafting session sevoflurane was applied by irrigation to the wound. Sevoflurane is an inhalation anesthetic agent of the group of halogenated ethers for use in induction and maintenance of general anesthesia. In its liquid form, sevoflurane can be used off label as a local anesthetic and applied by irrigation to painful wounds (8-10). Although studies

published in the literature are mostly isolated cases or short series, the results are promising (8-10). The benefit of topical sevoflurane does not seem to be limited to its analgesic effect, as it has been proposed to produce accelerated healing due to its vasodilator effect and, although its mechanism of action is unknown, bactericidal action has been detected in vitro against multidrug resistant strains of *S. Aureus*, *P. Aeruginosa* and *E.Coli* (8-10). The benefit/risk profile is very favourable since, as side effect, only itching and perilesional erythema have been described after application. Although sevoflurane blood levels have not been measured, no systemic effects have been recorded after local use (8-10). Consequently, topical sevoflurane may help to control pain and improve wound bed conditions before punch grafting without the need for surgical debridement (10).

In fact, as we commented that these ulcers can worsen with debridement, although most studies on the use of sevoflurane in wounds focus on its analgesic effect before debridement, we use it for its analgesic and vasodilator effect, without the need for debridement. More studies are needed to explore this hypothesis.

Among other aspects that require further research are the amount of sevoflurane and the frequency of irrigation most suitable for this type of wound, as well as how long to wait between sequential grafts. In fact, we usually space sequential grafts every 3 weeks, but there are no studies on the ideal interval between surgical procedures.

Regarding the limitations of the study, pain reduction at each treatment was not measured with the VAS scale, since it is not a simple tool for the elderly. Another limitation is that we did not record how quickly opioids were discontinued after treatment.

Even if this is a small sample, which is a limitation of the present results, this experience with this strategy in these arteriopathic ulcers in the authors' clinics shows similar results.

Conclusions

Considering the spectrum of arteriopathic ulcers, which should include Martorell ulcer and wounds in the context of age-associated arteriolosclerosis, the combination of topical sevoflurane and sequential punch grafting is of high interest for

The combination of topical sevoflurane and early sequential skin grafting reduces pain and promotes epithelialization

promoting healing, reducing pain, and avoiding lesion progression.

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Conflicting interest

None.

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