# Fat grafting and skin grafting for the treatment of non-ischaemic ulcers in the lower extremity

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## Summary

**Introduction:** Standard surgical treatment for non-ischaemic ulcers in the lower extremity often fails and its results become unpredictable. We present and evaluate the fat grafting technique that we use for the treatment of these wounds, to which we add a skin graft and negative pressure therapy.

**Material and methods:** This is a prospective case-control study of 46 patients with venous and vasculitic ulcers in the lower extremity. Thirteen patients were submitted to this surgical technique, and 33 were treated conservatively. We analysed the results of complete wound closure and size reduction. We compared these groups according to the presence of risk factors, and analysed the individual influence of each treatment and risk factors in the final result.

**Results:** In the surgery group, we achieved size reduction in 83.3% of the ulcers, and complete closure in 58.3% of them, in a mean time of 13.43 weeks. Surgical treatment managed to heal completely 100% of ulcers with an initial size of < 20 $cm^2$, but only 25% of those ≥ 20 $cm^2$ ($p = 0.016$). None of the included variables had a significant individual prognostic value in the final result. However, ulcers with complete closure had smaller mean size, regardless of the treatment ($p = 0.076$).

**Conclusions:** The effectiveness of the therapy may be dependent on the size of the ulcer. Fat grafting is an easy and safe procedure for the treatment of non-ischaemic chronic wounds in the lower extremity, but we cannot declare that this technique is more effective than conservative treatment for the healing of this type of wound.

**Key words:** leg ulcer, fat grafting, chronic wounds, skin grafting.

## Introduction

Chronic wounds have a high prevalence in the Western population (1–2%), 60–80% of which are venous ulcers [1, 2]. The treatment of chronic ulcers requires a lot of time and healthcare resources [1, 3], and causes a burden to patients. In the case of non-ischaemic ulcers, processes such as blood stagnation (venous ulcers) or vasculitis (autoimmune) are those that induce a decrease in tissue perfusion and oxygenation. This results in the breakdown of skin barriers and wound formation [2, 4, 5].

Chronic ulcers are often refractory to conservative and surgical treatments [3]. The standard surgical treatment for non-ischaemic ulcers in the lower extremity is debridement and coverage with autologous tissue, usually skin grafting [6, 7]. However, these techniques often fail, making the surgical treatment of these wounds unpredictable [8, 9]. Autologous fat transplantation in the form of a graft has its proven effect on tissues [10]. In recent years, autologous fat transfer has been reported for the treatment of chronic wounds, mainly in the lower extremity [7, 11].

Adipose tissue contains adipocytes and a compendium of additional cells, called stromal vascular fraction (SVF) [1, 4, 11, 12], that is comprised of adipocyte stem cells (ASC), among others. ASC are undifferentiated cells with the potential to transform into fibroblasts and endothelial cells, which are essential for wound healing [12–14].

The transfer of SVF in the form of a fat graft is a low-cost, widely used, simple technique with low morbidity [15, 16]. In this study we describe and evaluate the fat grafting technique that we use for the treatment of chronic wounds in the lower extremity, to which we add a skin graft and use negative pressure therapy.

## Material and methods

This is a prospective case-control study. All patients seeking assistance in our institution between 2018 and 2021 for lower leg non-ischaemic wounds were taking into consideration. In the cases group (surgery group) we included patients on whom the fat and skin graft tech-

nique was performed by the first author between 2018 and 2021. All procedures were performed in compliance with relevant laws and institutional guidelines and were approved by the institutional Ethics Committee.

The control group was formed by all other patients with the same pathology, but who underwent conservative treatment, without surgery. The inclusion criteria were as follows: ulcers in the lower extremity, of at least 2 months of evolution, without response to previous treatments (conservative or surgical). We excluded cases of ischaemic ulcers (patients with peripheral arterial disease) and patients with difficult follow-up (elderly, institutionalized, cognitive impairment).

On the first visit we evaluated the patient and the ulcers and took photographs with a scale to assess the size of the ulcer. If the patient presented more than one ulcer, we considered the sum of the surface area of each of them as the total surface area. After the anamnesis and examination of the patient and an explanation of the technique, we requested informed consent for their entry into the study.

No standard randomization method was applied. The patients themselves decided the treatment to receive, and therefore their entry into one of the groups.

Surgery was performed in the operating room with epidural anaesthesia. We performed fat aspiration and decantation, sharp wound debridement, and infiltration of the processed fat through the ulcer's edges. We then covered the ulcer with a split thickness skin graft (STSG) and sealed the graft over the ulcer with continuous vacuum-assisted therapy at –90 mmHg.

Conservative treatment consisted of periodic off-patient cures, performed by nurses in the patient's health centres, and in the case of venous ulcers, compression therapy was applied. The wound is covered with a non-adhesive dressing, and compression is applied with a multi-layered bandage system over the affected limb.

After the surgical intervention or the initiation of conservative treatment, we carried out the assessment of the ulcer's size by means of photographs with a scale, in each revision. The measurement was carried out with Image J (Research Services Branch, National Institute of Mental Health) software.

We analysed the results of complete wound closure, defined as stable and firm skin coverage in 100% of the ulcer surface; closure of more than 50% of the ulcer surface; and the total reduction in ulcer size. We divided the patients into 2 additional groups, based on whether complete wound closure was achieved in their case. We performed a univariate analysis comparing these 2 groups according to the following variables: age; sex; presence of risk factors including ischaemic heart disease (IHD), smoking, diabetes mellitus (DM), and body mass index (BMI) ≥ 30; and time from the onset of the ulcer and its initial size. We used the chi-square and Student's t statistics.

We performed a multivariate analysis using logistic regression to determine the individual influence of the treatment (surgical, conservative) and of each of the risk factor subgroups (IHD, smoking, DM, BMI ≥ 30) on the size of the ulcer. The analysis of the results was carried out with the SPSS 15.0 (IBM) computer program.

## Results

A total of 96 patients were taken into consideration, from which 46 met the criteria to be included in the study. From these, we subjected 13 patients to this surgical technique – 7 men and 5 women with a mean age of 59.75 years (range 35–75 years). The control group consisted of 33 patients – 15 men and 18 women, with a mean age of 76.33 years (range 46–96 years). The aetiologies of the ulcers were 44 venous and 2 autoimmune (vasculitis), with a mean area of 73.75 $cm^2$ (range 0.57–223.87 $cm^2$) in the surgery group and 23.14 $cm^2$ (range 0.65–89.28 $cm^2$) in the control group. Ulcers had a mean onset time of 127.3 weeks (range 8–612 weeks) in the surgery group and 46.76 (range 8–66 weeks) in the control group. In the surgery group we achieved size reduction in 10 of them (83.3%), a reduction of more than 50% of its surface in 9 (75%), and complete closure in 7 (58.3%). In the control group we observed size reduction in 32 of them (97%), a reduction of more than 50% in 27 (81.8%), and complete closure in 21 (63.6%) (Figs. 1–4).

We found no statistically significant differences when comparing these numbers between both groups ($p > 0.05$). In those cases in which we achieved complete closure, the mean time to achieve the result was 13.43 weeks (range 3–33 weeks) in the surgery group and 18.76 (range 4–66) in the control group ($p > 0.05$).

The results of the comparison between cases and controls, and the groups in which we achieved complete closure, and those in which we did not, are shown in Table 1. We found no statistically significant differences when comparing both treatments, or the variables age, sex, and presence of risk factors including IHD, smoking, DM, and BMI ≥ 30. We also found no significant differences when comparing the mean onset time of the ulcer or its initial size in each of the subgroups.

The multivariate analysis in which we included the group of treatment, risk factors (DM, smoking, IHD, BMI ≥ 30), age, sex, and ulcer size, showed that none of these variables had a significant individual prognostic value in the result. However, the ulcer size showed an inversely proportional tendency for closure, with a significance value of 0.076.

Thus, we made a comparison of the initial average size of the ulcers, regarding the result in each of the

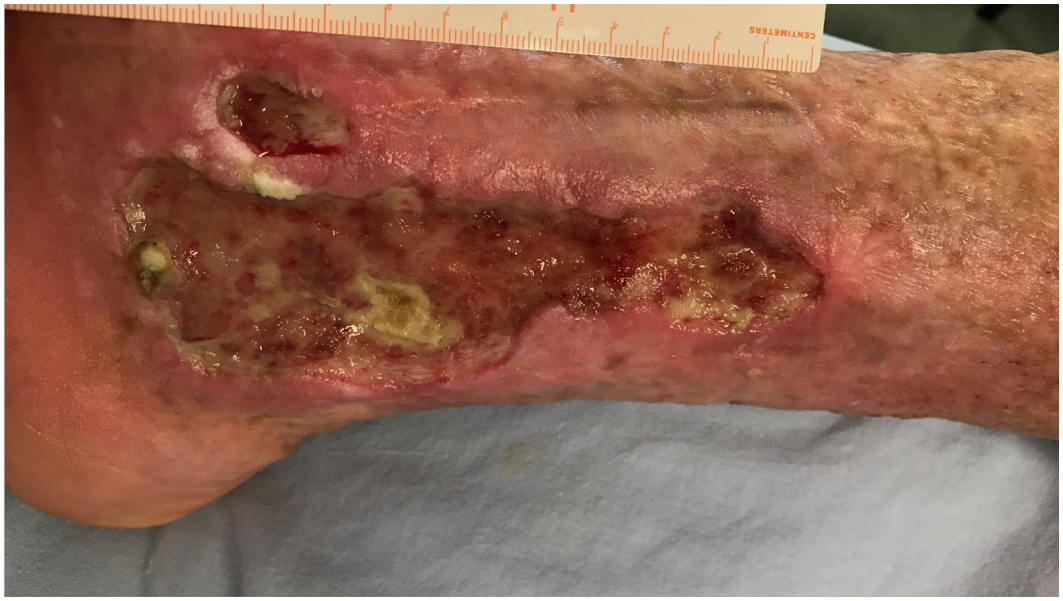

**Fig. 1.** Patient number 1, preoperatively. Left external malleolus ulcer

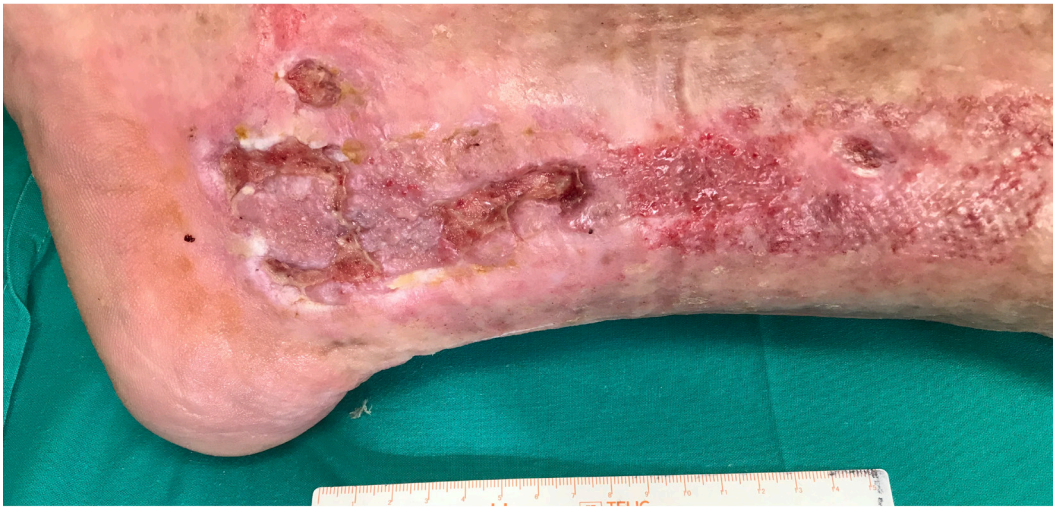

**Fig. 2.** Patient number 1, after 2 sessions of surgery. Left external malleolus

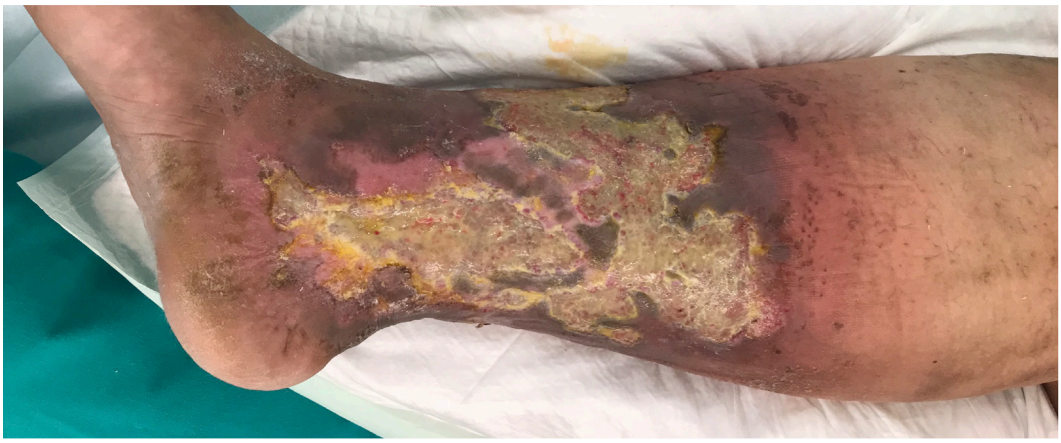

**Fig. 3.** Patient number 3, preoperatively. Right leg

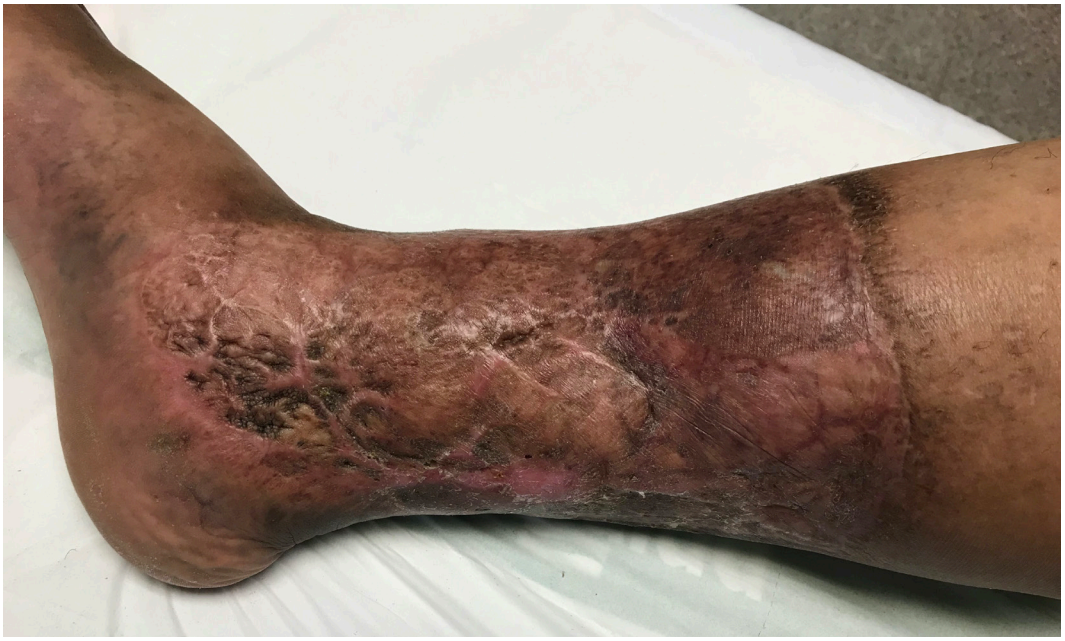

**Fig. 4.** Patient number 3, 8 months after surgery

treatment groups. No statistical differences were found. However, when making this same comparison with the entire sample, regardless of the treatment, we observed that the ulcers in which we achieved complete closure had a significantly smaller mean size than those in which we did not (25.56 vs. 55.87 $cm^2$, $p = 0.05$).

In addition, in the surgery group we observed that we achieved complete closure in 100% of those with an initial size < 20 $cm^2$ (38.5% of the total of the group), but only in 25% of those with a size ≥ 20 $cm^2$ (15.4% of the total of the group) ($p = 0.016$). We did not observe these differences in the control group (Table 1).

## Discussion

Debridement and replacement of injured tissue with healthy tissue in the form of a STSG is still considered the gold standard in the treatment of chronic wounds [7]. However, failure of this therapy is common [3, 8]. As an alternative, some authors propose the use of free flaps to replace this diseased tissue [6]. In our work we report an example with a bad outcome. Hence there is a need to search for more effective techniques, especially in patients with complex wounds, who generally also suffer from multiple comorbidities [7]. Fat grafting in these wounds appears in the literature as a simple, safe procedure that solves the problem effectively [15, 16].

The regenerative potential of fat grafting is due to regenerative cell precursors present in the SVF of adipose tissue [1, 17–22]. Adipose tissue as a source of this type of cells has many advantages over other tissues, such as bone marrow, because it is easy to harvest [18, 19], it does not need culture or expansion [11], the morbidity of the donor area is minimal, it does not produce a foreign body response [23], and it does not generate ethical problems [14, 22].

All chronic wounds have poorly vascularized tissue. ASC in the SVF can differentiate into other tissues and to modify molecular signals [13, 14] to induce a vasculogenic effect [4, 17]. The contribution of SVF in the form of fat grafting to ulcers will produce a replacement of the damaged local vascularization by new vessels that nourish the graft and provide supplemental oxygen to the ulcerated tissue [4, 24, 25].

During the processes of fat harvesting, processing, and injection there are many factors that affect the collection and survival of this tissue [26]. The standard liposuction procedure, the Coleman technique [11, 27], has shown sufficient effectiveness in obtaining ASC from adipose tissue [12, 27, 28].

In previous studies that described similar techniques for the treatment of this pathology, some authors did not specify the initial size of the ulcers to be treated [1, 2, 12, 16–18, 20, 29], and in those that they did, we observed that the treated ulcers had a smaller mean size, i.e. between 5.1 and 54.9 $cm^2$ [8, 30–32]. In our study, the average area was 69.26 $cm^2$, with ulcers up to 223 $cm^2$ surgically treated. These differences may be because in our study we analysed the surface of the ulcers of a single patient as a whole, regardless of the number of ulcers present.

In these studies they also reported mean onset times of between 15.4 weeks and 26.57 months [8, 29, 31, 32]. In our study, the average onset time is over 30 months. We do not know the reason why consultation or referral to the plastic surgery service takes lon-

**Table 1.** Comparison between groups

| Parameter | Group | | Complete closure | | *p* |
|---|---|---|---|---|---|
| | | | Yes | No | |
| | Surgical treatment | | 7 (53.8) | 6 (46.2) | 0.387 |
| | Conservative treatment | | 21 (63.6) | 12 (36.4) | |
| Age, *n* (%) | Surgical | < 60 years old | 4 (30.8) | 1 (7.7) | 0.179 |
| | | ≥ 60 years old | 3 (23.1) | 5 (38.5) | |
| | Conservative | < 60 years old | 1 (3) | 0 (0) | 0.636 |
| | | ≥ 60 years old | 20 (60.6) | 12 (36.4) | |
| Sex, *n* (%) | Surgical | Male | 4 (30.8) | 3 (23.) | 0.689 |
| | | Female | 3 (23.1) | 3 (23.1) | |
| | Conservative | Male | 7 (21.2) | 8 (24.2) | 0.068 |
| | | Female | 14 (42.4) | 4 (12.1) | |
| Diabetes mellitus, *n* (%) | Surgical | Yes | 0 (0) | 2 (15.4) | 0.192 |
| | | No | 7 (53.8) | 4 (30.8) | |
| | Conservative | Yes | 9 (27.3) | 3 (9.1) | 0.261 |
| | | No | 12 (36.4) | 9 (27.3) | |
| Ischaemic heart disease, *n* (%) | Surgical | Yes | 0 (0) | 0 (0) | ** |
| | | No | 7 (53.8) | 6 (46.2) | |
| | Conservative | Yes | 3 (9.1) | 3 (9.1) | 0.374 |
| | | No | 18 (54.5) | 9 (27.3) | |
| Smoking, *n* (%) | Surgical | Yes | 2 (15.4) | 2 (15.4) | 0.657 |
| | | No | 5 (38.5) | 4 (30.8) | |
| | Conservative | Yes | 3 (9.1) | 0 (0) | 0.244 |
| | | No | 18 (54.5) | 12 (36.4) | |
| Body mass index, *n* (%) | Surgical | < 30 | 3 (25) | 4 (33.3) | 0.179 |
| | | ≥ 30 | 4 (33.3) | 1 (8.3) | |
| | Conservative | < 30 | 6 (18.2) | 3 (9.1) | 0.579 |
| | | ≥ 30 | 15 (45.5) | 9 (27.3) | |
| Onset time, *n* (%) | Surgical | ≤ 1 year | 4 (30.8) | 2 (15.4) | 0.383 |
| | | > 1 year | 3 (23.1) | 4 (30.8) | |
| | Conservative | ≤ 1 year | 20 (60.6) | 9 (27.3) | 0.125 |
| | | > 1 year | 1 (3) | 3 (9.1) | |
| Size, *n* (%) | Surgical | < 20 $cm^2$ | 5 (38.5) | 0 (0) | **0.016** |
| | | ≥ 20 $cm^2$ | 2 (15.4) | 6 (46.2) | |
| | Conservative | < 20 $cm^2$ | 14 (42.4) | 7 (21.2) | 0.456 |
| | | ≥ 20 $cm^2$ | 7 (21.2) | 5 (15.2) | |
| Mean onset time (weeks) | Surgical | | 88 | 173.17 | 0.374 |
| | Conservative | | 22.57 | 89.08 | 0.106 |

ger in our setting than in other centres referred to in the literature.

Regarding the results obtained as complete closure, other studies reported success rates with complete closure achieved in 65-100% of the treated cases [1, 2, 8, 12, 15, 16]. These figures are better than those obtained in our study, with a success rate of 53.8% for the surgery group and 63.3% for the control group. When comparing the groups according to the therapy used (surgery vs. conservative), we found no differences in the outcome variables (complete closure, > 50% closure or size reduction) between the 2 groups. We also did not observe differences in the time to achieve this result. We cannot speak of greater effectiveness of either of the treatments over the other.

According to the results obtained in our study, the initial size seems to have an influence on the result of the therapy. Thus, in the entire sample those ulcers

in which we achieved complete closure (regardless of the treatment performed) were smaller than those in which we did not (25.56 vs. 55.87 $cm^2$, $p = 0.05$). All the studies that we reviewed have in common that they either did not specify the size of the ulcers, or their sizes were under 10 $cm^2$. Thus, Raposio *et al.* reported the complete closure of 71% of 40 ulcers, with a mean size of 25.28 $cm^2$ [31], and Chen *et al.* achieved closure of 54% of their cases, in a size range of 25–120 $cm^2$ [32]. In our study we observed that we achieved complete closure in 100% of those with an initial size of less than 20 $cm^2$, but only in 25% of those over 20 $cm^2$ ($p = 0.016$). It is possible that the effectiveness of this technique is dependent on the size of the ulcers.

However, if we consider the reduction in the size of the ulcers as a positive and clinically acceptable result, we see that with this technique in our sample we achieved a reduction in the size of 10 out of 12 ulcers (83.3%), and a reduction of more than 50% in 9 of them (75%). In 2 of them the treatment was not effective, and we were unable to stop their progression. Progress in wound healing has been reported to decrease pain and improve quality of life in patients with this type of ulcer [33].

Previous studies reported disparate results regarding the time elapsed to achieve complete closure of these ulcers [2, 16, 17, 29, 30, 32], with the time ranging from 2 to 42.5 weeks. In our case, the mean was 13.43 weeks – a somewhat higher result than in other studies. This could be related to the larger size of the ulcers in our sample.

As a novelty, we incorporate the use of STSG to the technique described by Stach *et al.* [8]. Stach *et al.* proposed the possibility of using pinch micrografts as an adjuvant treatment [8]. No other work reviewed performs skin grafting at the same time as fat grafting [16, 32]. In our experience, the skin graft at the same time as the fat graft provides coverage and epithelial cells that also act as building blocks on which the fat can exert its paracrine effect. The main added complication of skin grafting is the morbidity of the donor area, which patients complain about due to occasional bleeding and discomfort during epithelialization by secondary intention.

## Conclusions

We cannot affirm that this surgical treatment is more effective than conservative treatment for the healing of this type of ulcer in the lower extremity. The effectiveness of treatment, both surgical and conservative, may depend on the size of the ulcer. Fat grafting is an easy, well-tolerated, and effective procedure for the treatment of chronic wounds, and it may represent a shift in the treatment paradigm of these injuries.

We are aware of the limitations of our study because of the small sample size, demographic differences among both sample groups, differences in the ulcers' aetiology and dimensions, and because it includes patients evaluated and treated during the COVID-19 pandemic, which may have produced alterations in the onset time of the ulcers and patient follow-up.

*The authors declare no conflict of interest.*

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