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## **Dermal substitutes in the treatment of venous ulcers**

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### **Abstract**

Venous ulcers are the most common ulcerative lesions of the lower limbs and represent a major clinical challenge, particularly in the geriatric population. Chronic cutaneous ulcers are frequently associated with cardiovascular and metabolic comorbidities, which impair tissue repair and prolong healing. Pain is the predominant symptom, resulting from exposure of deeper epithelial layers to inflammatory and irritative processes. Diagnosis relies on clinical evaluation, venous colour Doppler ultrasonography, and laboratory investigations. Treatment is guided by ulcer aetiology and includes compression therapy, advanced wound dressings, surgical debridement, negative pressure wound therapy, and dermal substitutes.

Because the extracellular matrix plays a dynamic role in tissue regeneration, therapeutic strategies emphasise wound bed preparation and acellular dermal matrices. These biomaterials provide a non-immunogenic scaffold that supports cell migration while avoiding donor-site morbidity. In a retrospective observational study of 62 patients with chronic cutaneous ulcers, predominantly venous, an integrated therapeutic approach combining surgery, selective debridement, and regenerative biomaterials resulted in clinical improvement in 71.29% of patients. Dermal substitutes were associated with a marked reduction in postoperative pain, with NRS scores decreasing from 6-7 to 0-3 overall.

**Key words:** chronic cutaneous ulcers, venous ulcers, wound healing, dermal substitutes.

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## **Introduction**

Venous ulcers represent the most common type of ulcerative lesion affecting the lower limbs. By distinguishing the main forms and etiologies of cutaneous tissue ulceration, it is possible to identify the following categories:<sup>1</sup> cutaneous ulcers associated with neoplastic diseases, pressure or decubitus ulcers, neurological disorders, or diabetes, which typically affect the lower extremities; vascular ulcers (venous, arterial, and mixed) - pain is the most common symptom of all ulcerative lesions and is related to the exposure of the deeper epithelial layers to inflammatory and irritative processes, resulting from increased sensitivity to mechanical, chemical, and infectious insults.<sup>2</sup>

Diagnosis is based on clinical assessment, venous color Doppler ultrasonography of the lower limbs - which represents the gold standard - and laboratory blood tests, including complete blood count, blood glucose levels, inflammatory markers, and protein profile.<sup>3</sup>

The treatment of ulcers depends on the underlying cause identified during the diagnostic process. Venous ulcers should initially be managed with compression therapy using elastic bandages, antiseptic dressings, and the application of healing and re-epithelializing ointments.<sup>4</sup>

Advanced wound dressings include hydrocolloids (which promote rehydration of dry lesions and support granulation tissue formation), hydrogels (which facilitate autolysis), polyurethane foam dressings (which create a water-repellent barrier while maintaining a moist wound environment), hydrofibers (which absorb exudate and are indicated for highly exudative lesions), alginates (with hemostatic properties), and semi-permeable films (transparent polyurethane membranes).<sup>4</sup>

In most cases, ulcers may also require surgical debridement in the operating room, as an important part of the wound bed preparation, and the application of Negative Pressure Wound Therapy (NPWT), which increases healing rates by promoting the formation of granulation tissue.<sup>5</sup>

Dermal substitutes, on the other hand, are tissue-engineered products of animal or human origin, that reproduce the structural and biochemical functions of the extracellular matrix. They are indicated in the treatment of chronic ulcers, as they are processed into three-dimensional structures with specific surface charge and porosity, providing a scaffold that supports re-epithelialization.<sup>6</sup>

## ***Objectives***

This retrospective observational study aims to: i) describe the demographic and clinical profile of a cohort of patients affected by chronic cutaneous ulcers; ii) analyze the distribution of ulcer types and the main associated comorbidities; iii) evaluate the dermal substitute treatments applied; and iv) examine postoperative clinical outcomes, with particular attention to lesion improvement, pain evolution, quality of life, and survival.

## **Materials and Methods**

A total of 62 patients undergoing treatment for chronic cutaneous ulcers were included in the study. Data were collected regarding age, Body Mass Index (BMI), sex, and comorbidities, including dyslipidemia, arterial hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, and chronic kidney disease.

Ulcers were classified as venous, post-traumatic, mixed, or related to peripheral arterial disease. Pain intensity was recorded using the Numerical Rating Scale (NRS, 0-10). Pre- and postoperative analgesic therapies (Non-Steroidal Anti-Inflammatory Drugs, NSAIDs; or opioids) were documented, as well as the type of regenerative or surgical treatment performed (dermal substitute grafting, debridement, negative pressure wound therapy, or combined procedures).

The patients treated with dermal substitutes required a single application (Figure 1). Final clinical outcomes were categorized as improvement, stability, or worsening. Closure of the ulcer or a two-thirds reduction in the area was considered improvement. Categorical variables were analyzed using absolute frequencies and percentages, while continuous variables were summarized using mean and median values.

## **Results**

The mean age of the cohort was 75.64 years, with a mean BMI of 26.68, indicative of moderate overweight. The most frequent comorbidities were dyslipidemia and arterial hypertension (66.13%), followed by diabetes mellitus (40.32%), coronary artery disease (37.1%), atrial fibrillation (17.74%), and chronic kidney disease (8.06%) (Table 1).

Venous ulcers represented the most prevalent ulcer type (62.91%), whereas post-traumatic ulcers accounted for 19.35%, mixed ulcers for 9.68%, and ulcers related to Peripheral Arterial Disease (PAD) for 8.06%. Preoperative pain levels were generally high, with mean NRS scores ranging between 6 and 7. NSAIDs were the most used analgesic therapy both preoperatively (58.06%) and postoperatively (58.06%), whereas opioid use was more limited, with an overall reduction in analgesic drug consumption following treatment (Table 2).

Among advanced treatments, the most frequently used biomaterial was a dermal substitute composed of porcine tendon collagen (Pelnac®) (66.12%), followed by debridement alone (16.13%) and the use of a plant-derived flowable collagen matrix (Vergenix®) (4.84%). The remaining procedures showed lower frequencies but reflected a multimodal therapeutic approach (Table 3).

Clinical outcomes demonstrated improvement in 71.29% of patients, stability in 28.71%, and no cases of worsening. No adverse events occurred.

Another relevant finding concerned postoperative pain, with a marked reduction in NRS scores (NRS 0–3 in 70% of patients) compared with preoperative values (NRS 6–7 in 75% of patients). Overall survival during follow-up was 75.81%. Importantly, deaths were not related to venous ulcers or their treatment (Table 4).

## **Discussion**

Chronic cutaneous ulcers represent a highly prevalent condition in the geriatric population and are closely associated with the presence of cardiovascular, metabolic, and vascular comorbidities. Aging, microcirculatory pathophysiological alterations, and the accumulation of systemic risk factors contribute to the chronicization of lesions and to a reduced therapeutic response.<sup>7</sup>

The etiopathogenetic event leads to damage of the extracellular matrix, which does not merely serve as a passive structural support for the cellular population, but rather functions as a dynamic organ that actively interacts with and modulates tissue repair processes.<sup>8</sup>

Therefore, the treatment of cutaneous ulcers should be aimed not only at addressing the underlying causes of the lesion but also at preparing the wound bed and stimulating tissue regeneration. In this context, the use of dermal substitutes finds its full rationale, as they reproduce the biochemical and structural characteristics of the extracellular matrix. Prior to their use, large soft tissue defects were managed with autologous skin grafts, with the burden of donor site morbidity. Recently, the use of acellular dermal matrices has broadened because of their characteristics (contain a framework of insoluble molecules such as collagen, elastin, fibronectin, retain signals that promote cells attachment, proliferation and migration, lack of immunogenicity).<sup>9</sup>

The analyzed population exhibited a high burden of cardiovascular and metabolic comorbidities, with a predominance of venous ulcers related to chronic venous insufficiency and moderate-to-severe pre-treatment pain levels. In this study it must be underlined that pain is reported as an outcome measurement and that the treatment reduced the pain score (from 6-7 to 0-3 in 70% of patients).

## **Conclusions**

The adopted therapeutic approach, based on the integration of surgical techniques, selective debridement, and regenerative biomaterials, was associated with significant clinical improvement in the majority of patients (71,29%) and a favorable safety profile.

However, the high prevalence of systemic comorbidities and advanced age underscores the need for an interdisciplinary management strategy aimed at optimizing tissue perfusion, controlling cardiovascular diseases, and effectively modulating pain. Future prospective studies with larger sample sizes will be necessary to validate the comparative effectiveness of different biomaterials and to define standardized therapeutic protocols.

Finally, a School of Phlebological Surgery can train young surgeons who can make important contributions to this field as well.<sup>10</sup>

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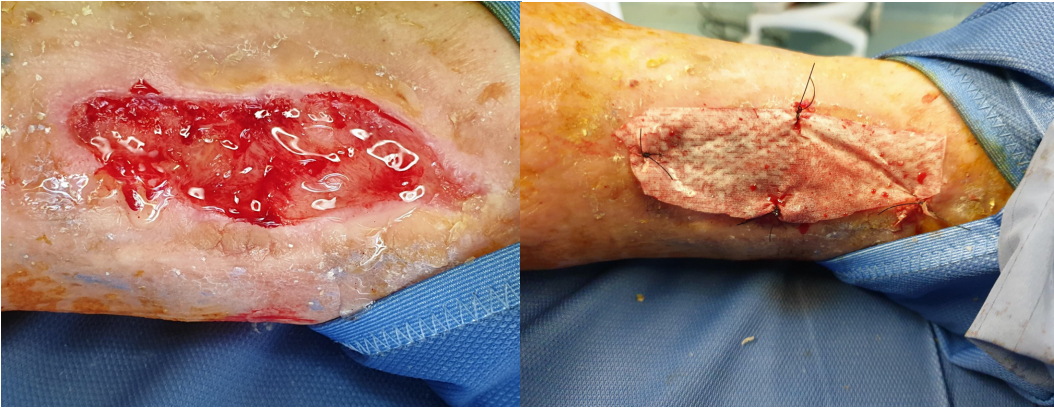
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**Figure 1.** Wound bed preparation and preparation of dermal substitute graft.

**Table 1.** Clinical and demographic characteristics of the study population.

<b>Total number of patients</b>	62
<b>Mean age (years)</b>	75.64%
<b>Mean BMI</b>	26.68%
<b>Male sex</b>	16.13%
<b>Female sex</b>	12.9%
<b>Dyslipidaemia</b>	66.13%
<b>Arterial hypertension</b>	66.13%
<b>Diabetes mellitus</b>	40.32%
<b>Atrial fibrillation</b>	17.74%
<b>Bedridden status</b>	0.0%
<b>Chronic kidney disease</b>	8.06%
<b>Coronary artery disease</b>	37.1%

**Table 2.** Ulcer characteristics, preoperative pain, and analgesic therapy.

<b>Post-traumatic ulcers</b>	19.35%
<b>Venous insufficiency ulcers</b>	62.91%
<b>PAD-related ulcers</b>	8.06%
<b>Mixed ulcers</b>	9.68%
<b>Preoperative opioid use</b>	25.81%
<b>Preoperative NSAID use</b>	58.06%
<b>Pre-treatment pain (NRS)</b>	6-7 >75% patients
<b>Mean length of hospital stay</b>	2 days in 51.61% patients

PAD, Peripheral Arterial Disease; NSAID, Non-Steroidal Anti-Inflammatory Drugs; NRS, Numerical Rating Scale

**Table 3.** Types of treatment administered.

<b>Pelnac®*</b>	66.12%
<b>Debridement</b>	16.13%
<b>Vergenix®*</b>	4.84%
<b>Flowable collagen matrix*</b>	3.23%
<b>Debridement + NPWT (VAC)</b>	3.23%
<b>Debridement + ligation</b>	3.23%
<b>Debridement + Pelnac®</b>	1.61%
<b>Versajet®*</b>	1.61%

\*Pelnac® is a bilayer dermal substitute composed of an atelocollagen sponge derived from porcine tendon collagen and a silicone outer layer. The collagen matrix acts as a scaffold for cellular infiltration, angiogenesis, and extracellular matrix deposition, thereby promoting dermal regeneration

\*Vergenix® is a plant-derived, recombinant human collagen-based dermal substitute produced through tobacco plant bioengineering. It consists of type I human collagen identical to native human collagen, but free from animal or human donor material. This biomaterial provides a biocompatible three-dimensional scaffold that supports cellular adhesion, migration, angiogenesis, and extracellular matrix deposition, thereby promoting tissue regeneration and wound healing

\*A flowable collagen matrix is an injectable or malleable three-dimensional biomaterial composed primarily of collagen, designed to fill irregular wound cavities and deep tissue defects. It provides a temporary extracellular matrix scaffold that supports fibroblast migration, neovascularisation, and granulation tissue formation

\*Versajet® is a hydrosurgical debridement system that uses a high-velocity, pressurised saline jet to selectively remove devitalised and necrotic tissue while preserving viable structures. The system operates according to the Venturi effect, enabling precise and controlled tissue excision with simultaneous irrigation and aspiration

**Table 4.** Post-operative outcomes and pain assessment.

<b>Post-operative improvement</b>	71.29%
<b>Post-operative stability</b>	28.71%
<b>Post-operative worsening</b>	0.00%
<b>Post-operative opioid use</b>	20.97%
<b>Post-operative NSAID use</b>	58.06%
<b>Survival (yes)</b>	75.81%
<b>Survival (no)</b>	24.19%
<b>Post-treatment pain (NRS)</b>	0–3 in 70% of patients

NSAID, Non-Steroidal Anti-Inflammatory Drugs; NRS, Numerical Rating Scale