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NOVELTIES IN DERMATOLOGY

Hair-follicle Transplant Into Chronic Ulcers: A New Graft Concept[☆]

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Células madre del folículo piloso;
Úlceras venosas de miembros inferiores;
Injerto punch;
Trasplante de pelo

Abstract Chronic venous leg ulcers are a major therapeutic challenge in clinical practice, and the search for new approaches to improve wound healing is essential. Many ulcers do not heal with traditional treatment using compression, debridement, and dressings. Skin-grafts variants, such as pinch grafts, punch grafts, split- or full-thickness skin grafts, and grafts derived from cells cultured in the laboratory, are among the most widely used options in ulcers that do not heal. In recent years, numerous studies have brought to our attention the important role of the hair follicle in the healing process of cutaneous wounds. Putting knowledge into practice, hair follicles from the scalp have been used in punch-type grafts transplanted to the base of chronic ulcers to stimulate healing. Results appear to be better than those with traditional hairless punch grafts, opening new lines of treatment for recalcitrant chronic venous ulcers.

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Trasplante de folículos pilosos en úlceras crónicas: un nuevo concepto de injerto

Resumen Las úlceras venosas crónicas de los miembros inferiores representan un reto terapéutico importante en la práctica clínica diaria, resultando primordial la búsqueda de nuevas alternativas que mejoren la curación de estas heridas. Pese al tratamiento habitual con compresión, desbridamiento y uso de apósitos, muchas úlceras permanecen sin cicatrizar. En estas úlceras que no curan uno de los tratamientos más empleados es el trasplante de injertos cutáneos en sus diversas variantes: *pinch grafts*, *punch grafts*, injertos de piel de espesor parcial, injertos de piel de grosor total e injertos elaborados a partir de células cultivadas en laboratorio. En los últimos años numerosos estudios han destacado el importante papel del folículo

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piloso en el proceso de cicatrización de las heridas cutáneas. Trasladando a la práctica estos conocimientos se han utilizado folículos pilosos del cuero cabelludo en injertos tipo *punch* que son trasplantados al lecho de las úlceras crónicas para estimular su curación. Los resultados parecen ser mejores que el trasplante tradicional de injertos tipo *punch* sin pelo, lo cual proporciona nuevas líneas de tratamiento para las úlceras venosas crónicas recalcitrantes.

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Introduction

Chronic venous leg ulcers are a common chronic medical problem that may be debilitating and have a substantial impact on the quality of life of the patient. Standard treatment of venous ulcers is based on use of adequate dressing along with effective compressive therapy.¹⁻³ Nevertheless, up to 20% of venous ulcers have not healed after 50 weeks of appropriate compression.⁴ For those patients who do not respond to conventional treatment, there are other therapeutic options such as intermittent pneumatic therapy,⁵ drugs (pentoxifilin,⁶⁻⁸ tretinoin,⁹ timolol,¹⁰ micronized purified flavonoid fraction,¹¹ heparin,^{12,13} doxycilin,¹⁴ and acetyl salicylic acid^{15,16}), autologous platelet-rich plasma,^{17,18} hyperbaric oxygen therapy,¹⁹ electromagnetic therapy,²⁰ and negative pressure therapy.²¹ Surgical options include venous surgery,^{3,22-25} and the use of skin grafts.¹

Skin Grafts in Chronic Ulcers

Skin grafts can be classified as autografts, allografts, or xenografts. Grafts can also be classified according to those composed of skin fragments, layers of laboratory-cultured cells, and wound dressings that incorporate skin cells.^{1,26}

Autografts are obtained from the same patient. Pinch grafts, punch grafts,²⁷⁻²⁹ partial-thickness skin grafts, full-thickness skin grafts, and grafts produced from laboratory culture of cells from the patient, such as cultured keratinocyte grafts have been used. Allografts are obtained from skin or cells of another person, which are cultured and prepared in the laboratory (cultured keratinocytes, cultured epidermal fibroblasts).^{30,31} Xenografts are obtained from an animal; pigs are the most frequently used animal, given the similarity with human skin.

In some studies, cure rates of 50% after skin grafting have been reported.^{3,32,33} Given the ease of access, the donor areas for grafts have always been the thighs, buttocks, or back.^{28,28} However, the traditional concept of grafts derived from skin from the buttocks or abdomen in the treatment of chronic ulcers has changed in recent years thanks to the publication of several studies that point to a connection between hair follicles, stem cells, and wound healing.³⁴⁻⁴⁴ As a result, new studies have used follicular grafts from the scalp as a new treatment option within the therapeutic arsenal for chronic ulcers.⁴⁵⁻⁴⁷

The donor area for the graft should meet a series of requirements such as the possibility of simple postoperative care, low risk of infection, rapid wound healing, and minimal residual scarring. The site that meets all these characteristics is the scalp.⁴⁸

Function of Hair Follicles in Wound Healing

Areas of skin with hair have been shown to heal more quickly than bald areas.⁴⁹⁻⁵¹ For example, areas of skin where radiotherapy⁵² has destroyed adnexal structures such as the hair follicles or eccrine glands⁵³ heal much more slowly.

The most important demonstration to date that hair follicles play a central part in healing is still the study published by Bishop⁴⁹ in 1945. This investigator inflicted skin wounds to different depths on his own arm and then took sequential biopsies to meticulously study the healing process. Skin healing started not just from the edges of the wound but around the remnant follicles. The study also showed that not only reepithelization but also regenerated granulation tissue started to form from the perifollicular connective tissue, suggesting a key role for hair follicles in initiating the wound healing process.⁴⁹

In 1939, Okuda⁵⁴ performed some histological studies of biopsies taken at different times during wound healing after hair grafting. This investigator detected proliferation of connective tissue cells from hair follicles implanted within the connective tissue of the recipient area.

Hair follicles are also known to represent the main reservoir for skin stem cells.⁵⁵⁻⁵⁷ In response to a skin wound, epithelial stem cells in the bulge region of the follicle proliferate and emigrate to the surface to contribute to reepithelization of the new epidermis.⁵⁰ Likewise, mesenchymal stem cells in the dermal sheath contribute to regeneration of dermal tissue.⁵⁸⁻⁶⁰ The scalp, given its high density of hair follicles in anagen phase, and the resulting high density of epithelial and mesenchymal stem cells, would theoretically be the ideal donor area for follicular transplantation to stimulate wound healing.

Several case reports have been published that support the contribution of hair follicles to wound healing.^{35,38,39,59,61,62} Most are isolated clinical cases of patients with burns or surgical wounds treated with a combination of skin substitute dressing and hair transplantation.⁶³⁻⁶⁵ Navsaria et al.⁶⁴ published the case of a patient with extensive and deep burns in the scalp who achieved complete wound healing after implantation of hair follicles on an artificial dermis (Integra, Integra LifeSciences Corporation, Plainsboro, N.J., US). Similarly, Narushima et al.⁶³ published cases of 2 patients with surgical defects in the scalp that were covered with artificial dermis (PELNAC, Smith & Nephew KK, Japan) and follicular units subsequently implanted in order to obtain hair growth and thus a more esthetic result. Zakine et al.⁶⁵ published a series of 15 patients with acute third-degree burns who were treated with dermal grafts of the scalp. This type of

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