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Use of Human Recombinant Epidermal Growth Factor in Chronic Wounds: Experience in Colombia - Review Article

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Abstract: *Epidermal growth factor is a 53 amino acid polypeptide that is produced by different cells such as platelets, macrophages, etc., which, by binding to its specific membrane receptor, generates a formation process and is activated in the cell, triggering processes that promote chemotactic activity, cell proliferation and angiogenesis, favoring healing processes.*

Currently, it is marketed as a human recombinant epidermal growth factor (rhEGF), a product obtained by genetic engineering, unique and the first of its kind, for injectable administration in chronic wound tissue, increasing the granulation and epithelialization process decreasing the time to achieve granulation compared to conventional therapies. We present a review of the experience with the use of this medication in chronic wounds, in Colombia, together with a review of related publications.

Keywords: *Chronic wounds, Epidermal growth factor, EGF, Human Recombinant Epidermal Growth Factor, rhEGF.*

INTRODUCTION

Epidermal growth factor is a polypeptide of 53 amino acids and 6 cysteine residues forming three disulfide bonds essential for receptor affinity (1). When EGF binds to its receptor (EGFR) on the cell surface,, dimerization of EGFR occurs followed by autophosphorylation of Tyr residues in the receptor's cytoplasmic domains. Phosphorylated Tyr residues initiate the cascade of events leading to the synthesis of DNA, RNA, and proteins (2). Through interaction with EGFR, EGF fulfills a variety of physiological functions related to mitogenic capacity in a wide variety of cell types: epithelial, hepatocytes and fibroblasts, being important in wound and burn healing, since this factor is secreted by platelets and macrophages that regulate inflammation and fibroblast action and stimulate the growth, proliferation, differentiation and survival of epithelial cells for tissue repair (3).

The availability of EGF and the development of stable formulations have allowed experimentation to determine the effects, possibilities, indications and safety of EGF as therapy and to allow its clinical use (2). Evidence show therapeutic uses of EGF in post-traumatic skin lesions, surgical wounds, (4) burns, vascular ulcers (including diabetic foot) (5), pressure ulcers (2) and for skin graft reinforcement (6) (7).

In the 1980s, some researchers from the Center for Genetic Engineering and Biotechnology in Havana, Cuba, managed to synthesize a recombinant version of this factor. Human recombinant epidermal growth factor (rhEGF) is available, derived from genetic engineering techniques, suitable for clinical use in the prevention or treatment of various skin disorders (8). This technology is available in Colombia since 2012 with the drug brand name EPIPROT of the company Praxis Pharmaceutical, in vials of 75 mcg which must be reconstituted in 5 ml.

This technology has become an advanced curative treatment for all chronic wounds that are difficult to manage and do not evolve in a proper granulation and epithelialization process, becoming a hopeful therapy for patients presenting who have received multiple treatments and have not achieved a wound satisfatory evolution.

CHRONIC WOUND CONCEPT

The skin is considered the largest organ in most vertebrate organisms, with a complex structure of three layers: the epidermis, the dermis and the hypodermis, which under normal conditions have the capacity for self-regeneration. This organ is involved in various biological processes, such as the regulation of body temperature, the support of blood vessels and nerves, the prevention of dehydration, sensory detection processes and works also as an external barrier against pathogens and chemical substances (9).

By definition, a wound is an alteration of the normal anatomical and physiological structure of a tissue, and represents considerable damage to natural defense barriers against foreign agents (9).

The term "chronic wound" was first found in the literature in the 1950s, to refer to wounds that were difficult to heal or that did not follow the normal healing process, thereafter, the term has evolved over time, with other authors including that a period of more than 3 months must have elapsed without healing (10).

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CHRONIC WOUND EPIDEMIOLOGY

Chronic wounds affect 1% of the adult population, 3.6% of people over 65 and more than 5% of people over 80 (11).

Throughout their lives, nearly 10% of the population will develop a chronic wound, with a 2.5% wound-related death rate (12)

20% will not heal ≤2 years, and approximately 8% will not heal after 5 years (13).

According to the Wound Healing Society, approximately 15% of older adults in the US suffer from chronic wounds, which mainly include venous stasis ulcers, pressure ulcers (bedsores), and diabetic (neuropathic) foot ulcers. Every year, 2 to 3 million more Americans are diagnosed with various types of chronic wounds (14)

The incidence of chronic wounds is increasing as a result of an aging population and an increase in risk factors such as smoking, obesity, and diabetes. (15).

The immense economic, social and quality of life impact of patients suffering from chronic wounds requires the allocation of a higher level care (16).

CHRONIC WOUNDS ETIOLOGY

The etiology of chronic wounds can be diverse:

1. Neoplasms, e.g. predominantly basal cell or epidermoid skin tumors

2. Infectious diseases such as cutaneous tuberculosis, leishmaniasis, Hansen's disease and deep mycoses

3. Related to hematology issues such as autoimmune diseases, e.g. sickle cel anemia, hypercoagulable states, thalassemia and polycythemia vera

4. And the most common types that correspond to more than 50% of chronic wounds, such as pressure wounds and wounds generated by vascular alterations, whether venous or arterial, and neuropathic wounds predominantly diabetic foot ulcers. (17).

MOLECULAR BIOLOGY OF CHRONIC WOUNDS

Under normal conditions, wounds will heal efficiently over time through an orchestrated progression of 4 overlapping major healing phases, including hemostasis, inflammation, proliferation, and remodeling (18).

When a wound gets stuck at the inflammatory phase and do not advance in the healing process it becomes a chronic wound. Therefore, the objective is to make the wound move forward to the next healing phases.

It is important to point out that monocytes that reach the wound site then differentiate into macrophages. First, into M1 macrophages that are predominantly pro-inflammatory and feature phagocytosis and bactericidal capacity. As the wound is processed and the number of bacteria is reduced to levels compatible with healing, monocytes will then differentiate into M2-type macrophages that which promote the production of anti-inflammatory cytokines (e.g. L10) and produce and secrete growth factors such as the transforming growth factor beta and the epidermal growth factor, among others. Therefore, M2 macrophages are pro-healing and anti-inflammatory. (19, 20).

In acute wounds, neutrophils and M1 macrophages are found in the initial inflammatory phase, but as the wound is processed and biological burden is reduced, the wound advances to the late inflammatory stage, where only M2 macrophages will be found. (21).

However, in chronic wounds, what a significant increase in the number of neutrophils and M1 macrophages is observed, but there are no M2 macrophages, this is then an environment in which M1 neutrophils and macrophages are producing large amounts of free radicals of oxygen and proteases that prevent wound healing. (22)

Therefore, there is a common molecular pathology for any type of chronic wound, regardless of its etiology, which maintains a biochemical environment that promotes the chronicity of these lesions due to the prolongation of the inflammatory phase and growth factor deficits, in addition, repetitive tissue damage occurs in most of these wounds, for example, ischemia with hypoxia and tissue necrosis, and an increased biological load of bacteria and biofilms that cause neutrophils and M1 macrophages, as well as mast cells to continue secreting these pro-inflammatory cytokines, e.g. TNF alpha or interleukin 1 and 6, and these attract more and more M1 macrophages that activate and secrete more proteases and free radicals, generating a vicious circle where growth factors and receptors, as well as the components of the extracellular matrix, begin to destroy themselves, and this results in a decrease in proliferation and a decrease in cell migration that is clinically considered to be an acute wound that becomes a chronic wound that does not heal (21, 22).

The purpose of treatment should be to eliminate this biological cascade of inflammation, proteases, and destruction of essential proteins for healing. Therefore, providing factors for which there is a deficit in these wounds such as growth factors would be of great importance to achieve rapid and adequate healing.

Management of chronic wounds has varied over time from the use of plasters in ancient times to passive dressings, wet healing and, subsequently, bioactive dressings, but these elements do not provide the essential factors that are not present in the healing process.

That is why it is important to scale the therapies and provide a more advanced treatment that provides the necessary precursors that generate the stimulus to

continue with the healing phases when these patients have been resistant and have had an unfavorable evolution to conventional treatment without achieving adequate healing of their wounds, being patients with multiple treatments, whose injuries are taking a long time to heal.

COLOMBIAN PUBLICATIONS ON THE USE OF THE HUMAN RECOMBINANT EPIDERMAL GROWTH FACTOR IN CHRONIC ULCERS

Epiprot is a human recombinant epidermal growth factor (rhEGF) available in Colombia. It is developed by Praxis Pharmaceuticals and commercialized in vials of 75 mcg.

It counts on a Sanitary Registry that allows its use as an adjuvant in epidermal regeneration processes in skin ulcers, ulcers of vascular origin and diabetic foot ulcer in stages 3 and 4 of the Wagner classification with an area greater than 1 cm2. (23).

Experience in Colombia has been very favorable in achieving granulation and epithelialization processes in a short time.

Specialists in plastic surgery, orthopedics, internal medicine and vascular surgery, use human recombinant epidermal growth factor in various chronic pathologies or complex wounds.

Several publications on the use of human recombinant epidermal growth factor in patients with chronic ulcers are available.

The first article on this subject was published in 2018 by the department of Plastic Surgery (Espitaleta et al) (24). It reported a case of a 47-year-old male patient who entered the emergency room after suffering a high-voltage electrical burn in a work environment. It was a second degree burn, with an extension of 60%, which required multidisciplinary treatment by internal medicine and plastic surgery services with a critical medicine intervention at the time the patient entered. The patient presented metabolic complications due to a confirmed infection by Pseudomona Aeruginosa, and received adequate support and antibiotic therapy, performing a tangential escharotomy, surgical exfoliation and debridement, thoracic fasciotomy and administration of human recombinant epidermal growth factor to improve epithelialization with good functional and aesthetic results. Figure -1 and Figure-2

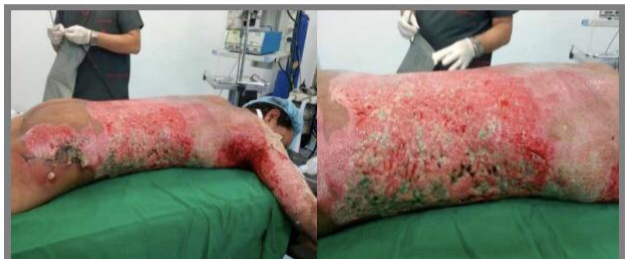

Figure 1. Patient with electrical burns

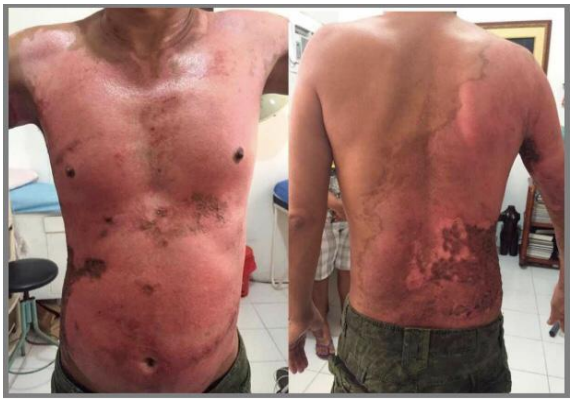

Figure 2. Final result of the patient with adjuvant rhEGF management.

Later in 2018, the department of Vascular Surgery carried out an observational descriptive study (Cacua et al) (25), a case series of 28 patients diagnosed with chronic venous ulcers of the lower extremities of more than 4 weeks of evolution, obtaining 35 ulcers. Patients were treated in two institutions in Bogotá with the purpose of evaluating the effectiveness of perilesional and intralesional use of human epidermal growth factor in the closure of chronic venous vascular ulcers in patients diagnosed with venous insufficiency CEAP VI in neuropathic, arterial, or mixed ulcers or with evolution of less than 4 weeks.

Analysis of the data obtained from this case series indicated that the use of intra and perilesional human recombinant epidermal growth factor in the treatment of venous ulcer achieved complete granulation in 100% of cases, 100% epithelialization in in 69% of the cases and an overall improvement rate of 86% in the short term (less than 8 weeks) was obtained, reducing the healing time of the wound and showing that this therapy is useful and favors healing. Figure 3.

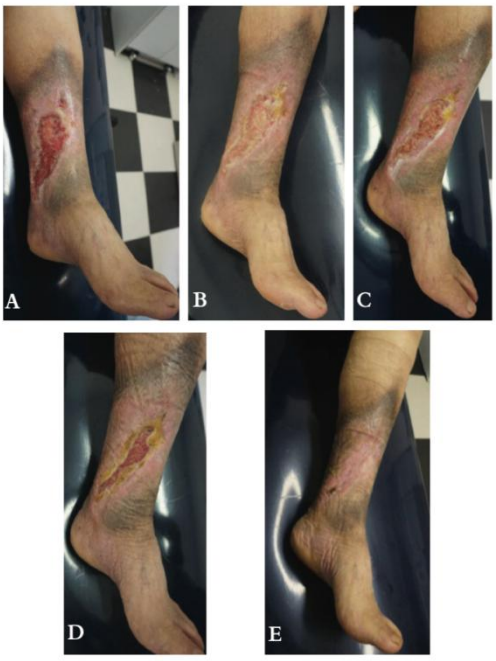

Figure 3. Patient with venous ulcer treated with rhEGF

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In 2019, the Vascular Surgery group in the city of Barranquilla (Daza et al) (26) published a case report, reporting 3 cases of complex vascular lesions, 2 diabetic foot ulcers and one mixed chronic wound of more than 4 years of multitreated evolution. Human recombinant epidermal growth factor was used in all 3 cases,, achieving total closure at 8 weeks in cases of diabetic foot and an epithelialization process of 90% and 95% granulation in the case of mixed chronic wound. Figure 4.

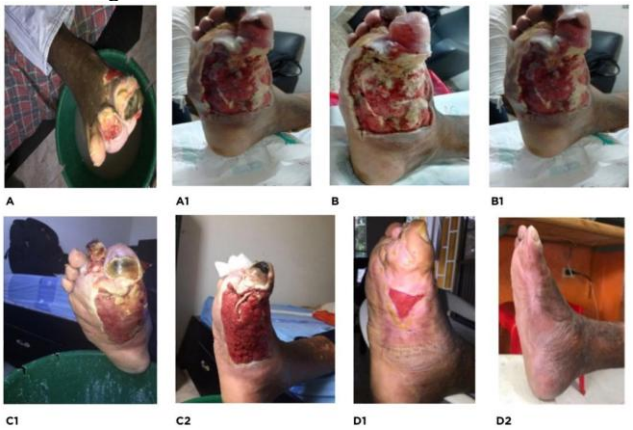

Figure 4. Patient with diabetic foot ulcer treated with rhEGF

In March 2019, the "Clinical Practice Guidelines for Diagnosis and Treatment of Patients with Complicated Diabetic Foot Wound" (27) was published, which was developed with the participation of multiple scientific societies of the country recommendations based on the evidence for the diagnosis and treatment of patients with complicated diabetic foot wound; recommendations were issued considering the risk-benefit relationship, the patient's preferences, the scientific evidence and the Colombian context. Later, recommendations were discussed and reviewed with a panel of experts and the patients representative, offering recommendations at two different degrees: Strong and Conditional, depending on the risk-benefit assessment, quality of evidence and Colombian context. 8 questions were asked; in regard with question 6 that corresponded to the effectiveness and safety of pharmacological interventions for the treatment of patients with complicated diabetic foot, the experts issued a Conditional recommendation and in favor of the use of human recombinant epidermal growth factor. Standardization of these Guidelines, which have been widely embraced by all medical and surgical specialties for the treatment of these patients, is in process in Colombia.

In addition, a cost-effectiveness analysis of the use of human recombinant growth factor in patients with diabetic foot ulcers was also performed (28), whose objective was to determine the cost-effectiveness ratio of intra and perilesional administration of human recombinant epidermal growth factor (rhEGF) versus conventional therapy for the treatment of patients diagnosed with Wagner diabetic foot ulcer using a Markov model, the care process of a diabetic patient diagnosed with Wagner 3 or 4 ulcer was configured with conventional treatment vs rhEFG. Treatments were evaluated weekly over a 5-year horizon; evaluated results are quality-adjusted life years (QALYs) and the number of amputations avoided by each treatment scheme, in addition to the total cost of the treatments. It was observed that the use of human recombinant epidermal growth factor resulted in 39 fewer amputations, in a cohort of 100 patients, compared to conventional treatment.

Similarly, 0.65 more quality-adjusted life years were observed with the use of rhEGF in an average patient. The estimated cost-utility ratio for the base case is below the threshold established for Colombia.

Currently there are 3 studies in their initial phase. In the first study (Cacua et al), quality of life in patients with chronic venous-type wounds will be measured applying the Charing Cross Questionnaire,, diabetic foot ulcers will be measured applying NeuroQol and other chronic ulcers will be measured applying the WoundQol at the beginning and end of rhEGF treatment.

The second study (Cacua, Bustamante et al) is a retrospective study that is being carried out in real life in patients belonging to two different health regimes in Colombia contributory and subsidized for sociodemographic characterization in patients with venous ulcers and their evolution in time taking into account the treatments performed, the percentage of infection, the use of antibiotics, the use of antidepressants, the number of specialized medical evaluations, the type of treatment, the healing time that will allow determining possible complications of this pathology based on of the treatment performed, conventional therapy or advanced management with rhEGF.

The third study is carried out by the Plastic Surgery team (Mendoza et al). It is a retrospective study of 20 patients with venous ulcers of more than 4 years of evolution that underwent joint treatment with rhEFG and partial thickness skin grafts.

CONCLUSIONS

Considering treatment with human recombinant epidermal growth factor (rhEFG) which can penetrate the biofilm and wound bed intralesionally and provide the structural support that is usually provided by the body, and which allows wound epithelialization is necessary and essential as an efficient therapy in the management of chronic skin wounds to shorten the wound healing process.

However, it is important to emphasize that the management of these patients must be comprehensive since the healing process is affected not only by wound factors, but also by paient-related factors, the correct

management of the etiology and their nutritional status, psycho-social factors such as social isolation, sex, financial situation and pain. Therefore, an interdisciplinary approach that involves other medical specialties and all necessary resources should be beard in mind when treating wounds.

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