

REVISIÓN

Conceptualization and approach to the main aspects related to post-phlebotic ulcers from a pedagogical-scientific-technological approach

Conceptualización y abordaje de los principales aspectos relacionados con úlceras posflebiticas desde un enfoque pedagógico-científico-tecnológico

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ABSTRACT

Introduction: Science is a systematic set of knowledge about objective reality, obtained through a specific form of action, called the scientific method. The first approach to science is considered as a form of social consciousness, that is, as a way for man to understand the world with an ethical and bioethical approach. It is made up of three elements: content, field of action, and procedure or way of acting.

Objective: to conceptualize the main aspects related to post-phlebotic ulcers from a pedagogical-scientific and technological approach.

Method: the specialized search of the bibliography was carried out between the months of 2018 and January 2024; The most outstanding articles in prestigious databases were selected, of which 90 % were published in the last five years.

Conclusions: the updated acquisition of knowledge on the methodological aspects of postphlebotic ulcers allowed, from the evidence, to review the possibility of achieving tissue regeneration through platelet- and leukocyte-rich fibrin, counting on an autologous biomaterial, to the simple and rapid ways to obtain it. The current state of knowledge in this transdisciplinary field suggests the design of projects that provide research outlets in this disease.

Keywords: Postphlebotic Ulcers; Fibrin; Pharmacokinetics; Platelets; Leukocytes.

RESUMEN

Introducción: la ciencia es un conjunto sistemático de conocimientos sobre la realidad objetiva, obtenidos mediante una forma específica de actuación, llamada: método científico. La primera aproximación entonces a la ciencia, es considerada como una forma de conciencia social, es decir, como una forma que el hombre tiene para conocer el mundo con un enfoque ético y bioético. La configuran tres elementos: el contenido, el campo de actuación y el procedimiento o forma de actuar.

Objetivo: conceptualizar los principales aspectos relacionados con úlceras posflebiticas desde un enfoque pedagógico-científico y tecnológico.

Método: la búsqueda especializada de la bibliografía se realizó entre los meses de 2018 a enero 2024; se seleccionaron los artículos más destacados en prestigiosas bases de datos, de los cuales el 90 %, fueron publicados en los últimos cinco años.

Conclusiones: la adquisición actualizada del conocimiento sobre los aspectos metodológicos de las úlceras

posflebiticas permitió, desde la evidencia, revisar la posibilidad de lograr la regeneración tisular a través de la fibrina rica en plaquetas y leucocitos, contando con un biomaterial autólogo, hasta las sencillas y rápidas vías para su obtención. El estado actual del conocimiento en este campo transdisciplinario sugiere el diseño de proyectos que den salidas en investigaciones en esta enfermedad.

Palabras clave: Úlceras Posflebiticas; Fibrina; Farmacocinética; Plaquetas; Leucocitos.

INTRODUCTION

Science is a systematic body of knowledge about objective reality obtained through a specific form of action called the scientific method.⁽¹⁾

The first approach to science is considered a form of social consciousness, that is, as a way for man to understand the world from an ethical and bioethical perspective.⁽²⁾

It comprises three elements: content, field of action, and procedure or way of acting.⁽³⁾

In terms of its content, science is made up exclusively of a body of knowledge about reality in the form of concepts and statements. The ideas in this body of knowledge are interrelated or systematized and form a theory. The unique field of action of science is an objective reality, the reality of this world we live in.^(3,4)

To have an up-to-date understanding of the aspects that govern the conceptual and theoretical framework of the diseases that find their possible solution in regenerative medicine, it is essential to clarify the concepts of science, technique, and technology, terms that encompass both the activity (research, development, execution, etc.) and the resulting product (knowledge, goods, services, etc.), and which are consequences of man's concerns and needs.^(5,6,7)

The first approach to science, then, is considered a form of social conscience, that is, a way for man to understand the world.

It consists of three elements: content, field of action, and procedure or way of acting.

In terms of its content, science is made up exclusively of a body of knowledge about reality in the form of concepts and statements. The ideas in this body of knowledge are interrelated or systematized and form a theory. The unique field of action of science is an objective reality, the reality of the world in which we live.⁽⁴⁾

In their actions, doctors must master these fundamental aspects to behave appropriately. Vascular skin ulcers (hereinafter referred to as ulcers for this paper) are classically and schematically divided into a) arterial (generally ischemic), b) venous due to venous hypertension, and c) mixed with both components. Venous ulcers are the most frequent (80 % of the total) and the most recurrent. The term venous ulcer encompasses both varicose ulcers and post-thrombotic or post-phlebotic ulcers. The former are more frequent because there is more varicose than thrombotic disease; however, during the evolution of a post-thrombotic syndrome, the appearance of an ulcer is more probable than with simple varicose disease.^(8,9,10)

This makes it impossible to perform multiple tasks. The research aims to conceptualize the main aspects related to post-phlebotic ulcers from a pedagogical, scientific, and technological perspective.

METHOD

To compile this article, the databases included in the LILACS, EBSCO, and HINARI services were consulted, and good availability was achieved in Cuba, Latin America, and the rest of the world. Websites of obligatory consultation due to their prestige and leadership on the subject were also visited, using the terms ethics, risk factors, bioethics, and science. An initial bibliographic search was carried out to address the ethics and conceptualization of science and ulcers. In the second stage of the review, the terms used to search were expanded. Those articles were included, which, through different terms, addressed bioethics in the care of the disease with a focus on its repercussions as a health problem, as well as others that, from the point of view of communication, could be beneficial or harmful for this type of behavior. The DeCS-controlled language was consulted to develop the search strategies, and the corresponding Boolean operators were included.

DEVELOPMENT

The word technology dates from the 18th century. When historically empirical technique began to be linked to science pro, duction methods began to be systematized.⁽¹¹⁾

Technology uses the scientific method, which comprises systematized knowledge, and in its actions, it operates in both the practical and conceptual spheres, encompassing technical production and its theoretical reflection. It results from relating techniques to science and economic and sociocultural structures to solve concrete problems.⁽¹²⁾

Venous ulcers are a paradigm of how morphological alteration (valvular insufficiency) conditions a functional alteration (venous reflux), whose physiopathology (venous hypertension) explains the clinical picture: ulcer and its manifestations.⁽¹³⁾

Once the ulcer has been identified as venous, its treatment involves several sequential stages, ranging from a conservative approach to surgery. Conservative treatment will be the first to be applied, with the aim of controlling the infection and promoting healing. This is achieved by combining a dry or wet local healing technique with another that controls venous hypertension, a compression-restraint technique, and/or postural treatment.

Pathophysiology

Venous ulcers are the most significant complication that can arise during CVI, both in the varicose syndrome of the superficial venous system and in the long-term evolution of venous hypertension caused by the sequelae of deep vein thrombosis, the so-called post-thrombotic syndrome. It is, without doubt, the most disabling complication and the one that has the most tremendous negative socioeconomic impact, being responsible for significant absenteeism from work and repercussions on quality of life.⁽¹⁴⁾

It is generally accepted that the macrocirculatory alterations secondary to CVI are transmitted to the microcirculation, and these latter alterations are responsible for the appearance of venous ulcers.⁽¹⁵⁾

Recent physiopathological studies of microcirculation reveal that a series of phenomena are involved in the process of tissue damage, such as the trapping and sequestration of leukocytes at the capillary level, with the production of free radicals and enzymes responsible for tissue damage and the inflammatory reaction that accompanies the formation of the ulcer. All these phenomena are ultimately the result of the local effects of venous hypertension and the tissue hypoxia caused in the affected area.⁽¹⁶⁾

Characteristics of post-phlebotic ulcers

A wide range of biological tests and instrumental support (echo-Doppler, arteriography, phlebography, etc.) are available to help establish and facilitate an accurate diagnosis of the underlying disease. However, in most cases, a good clinical history and a proper examination, paying attention to the location of the lesion, the presence or absence of accompanying pain, the appearance of the edges and bottom of the lesion, and the perilesional trophic disorders, as well as the possible concomitant diseases of the patient, usually lead us to know the origin of the lesion.^(17,18)

It is essential to describe the characteristics of the ulcer, as this can guide an initial approach to diagnosis, evolution, and therapeutic attitude, highlighting:

- The shape: circular, geometric, irregular.
- The location
- The size is necessary to monitor evolution.
- The edges: sharp, pitted, abrupt, necrotic
- The background: with granulation tissue, inflammation, slough, and necrotic material.
- The peri ulcerous area: with ochre dermatitis, varicose veins, eczema, edema, lymphadenopathy, and inflammation.

It is considered that before considering any type of treatment, local or general, that contributes to the healing of a trophic lesion of vascular etiology, an etiological diagnosis must be made to establish the therapeutic bases that will promote healing. Many vascular etiological processes can cause an ulcer. However, there are basic forms that are most frequently seen in outpatient consultations (table 1): venous, ischemic, neuropathic, hypertensive, and vasculitic ulcers.

Table 1. Differential diagnosis of lower limb ulcers

	Phlebostatic	Ischemic	Neuropathic	Arterial hypertension	Vasculitic
Location	Lateral internal	Variable	Lateral/plantar	External lateral	Anterolateral
Morphology	Lower 1/3	Irregular	Of the foot	Lower third	leg
Edges	Oval	Flat	Circumferential	Irregular	Circumferential
Background	Well defined	Fibrinoid	Calloused	Flat/irregular	Flat/well defined
Symptomatology	Fibrinoid	Very painful	Granular tissue	Fibrinoid	Hyperemic
Position	Not very painful	Symptoms worsen	Painless	Very painful	Variable

Note: Taken from Guimarães et al.⁽¹⁹⁾

AHT: Arterial Hypertension

The fundamental cause of these ulcers is a deterioration of cutaneous microcirculation due to venous

hypertension and hypoxia originating in the CVI of both superficial veins (varicose veins) and deep veins (post-thrombotic syndrome). This is a very characteristic appearance.⁽¹⁹⁾

Location: Generally on the medial aspect of the leg, above the ankle.

Characteristics: Rounded or oval, with regular edges, well-defined and sunken, with a variable depth. They tend to vary in size and can occupy the entire ankle circumference. They are not very painful or painless, except if they are infected. The skin surrounding the ulcer usually presents the cutaneous manifestations of CVI (hypodermatitis, ochre dermatitis, accompanying eczema). The spontaneous evolution of the untreated ulcer is superinfection and the growth of outbreaks of peri-ulcerous necrotizing lymphangitis.

Diagnostic suspicion: Diagnosis is usually based on the characteristics of the ulcer in the clinical context of a patient with clinical manifestations of varicose veins, a history of deep vein thrombosis and cutaneous dystrophy, and the presence of distal pulses in the absence of diabetes and hypertension.

Treatment of post-phlebotic ulcers

Chronic ulcers have a duality in their treatment: that of the underlying disease and local treatment. Etiological treatment is necessary but will not always solve the problem.⁽²⁰⁾

Cleaning the wounds is the essential link for successful healing. It is not a purely mechanical act. The success or failure of the healing will depend on its correct realization. The American Agency for Health Care Policy and Research (AHCPR) has used standards for cleaning pressure ulcers, which can be extended to other chronic ulcers. The use of antiseptics is a controversial issue since, as mentioned above, their use can be harmful.⁽²¹⁾

In standard medical practice, there are aspects to the management of a chronic ulcer with suspected infection:

1. In the case of clinical suspicion of infection (lousy smell, abundant or purulent exudation, abnormal granulation tissue, pain, cessation of the healing process, etc.), a culture with antibiogram should be taken by aspiration or biopsy.
2. The isolation of various germs does not necessarily indicate infection or interfere with wound healing; only the isolation of more than 10⁵ colonies/g indicates infection and an indication for treatment with systemic antibiotics.
3. Topical antibiotic therapy should be considered for ulcers that do not respond adequately to correct topical treatment:
 - Choose a broad-spectrum antibiotic effective against Gram-negative, Gram-positive, and anaerobic agents, such as sulfadiazine-silver.
 - Do not use dressings that do not allow gas exchange. Today, dressings generally contain silver or activated carbon and have bactericidal capacity.
 - No study has demonstrated the usefulness of local antiseptics in local infections; on the contrary, their use (povidone-iodine, sodium hypochlorite, hydrogen peroxide, acetic acid) is toxic for many of the cellular elements involved in the healing mechanisms. The AHCPR recommendations for cleaning ulcers include:⁽²²⁾
 - Cleaning should be the first step in treating the wound and always be carried out whenever the dressing is changed.
 - It should be carried out gently, using as little mechanical force as possible to allow the necrotic remains to be mechanically removed without causing trauma to the wound bed.
 - Do not use antiseptics such as iodine derivatives, sodium hypochlorite, hydrogen peroxide, or acetic acid
 - Use an isotonic saline solution

However, some molecules, such as iodine cadexomer, have proven to be valuable and non-toxic, and therefore, their use in chronic ulcers is not contraindicated.⁽²³⁾

This research is based on the consideration that the use of antiseptics is inappropriate given their known toxicity and aggressiveness on monocytes, fibroblasts, granulocytes, and granulation tissue, so instead, the use of physiological saline is recommended, which should be applied with a washing pressure of gravity itself or using a 35 mL syringe with a 0,9 mm needle with which a pressure of 2 kg/cm² is achieved. The safe pressure for washing ulcers ranges from 1 to 4 kg/cm².⁽²³⁾

Some authors consider debridement necessary for detritus, slough, or necrotic remains that are a breeding ground for the development of bacteria and demand a phagocytic response that is detrimental to wound healing. It can be carried out by mechanical, enzymatic, chemical, surgical, or even surgical methods using *Lucilia* sp. larvae (Diptera: Calliphoridae) obtained from eggs previously disinfected with sodium hypochlorite and sown in a culture medium with antibiotics.

Although this step is widely accepted and practiced, no studies demonstrate its effectiveness.⁽²³⁾

It is also essential to control exudate because, although the wound should be moist, it should not be too

wet as it could cause the edges and even the granulation tissue to become macerated. Excessive exudate can also be a sign of infection. There are now different types of dressings on the market that help to control ulcer exudate.⁽²⁴⁾

During the healing and re-epithelialization phases, it is advisable to maintain a moist and aseptic environment, which favors faster repair. It is also highly advisable to use dressings that allow for more frequent dressing changes, as this will prevent damage to the newly formed tissue.⁽²⁴⁾

Compression Therapy. Fundamental Basis

Compression therapy for venous ulcers, although an old method, is probably the most effective and cheapest treatment used to control hypertension and venous insufficiency, and its use is not incompatible with the use of different types of dressings or surgical therapy.⁽²⁵⁾

Compression therapy is considered to be the only effective treatment for chronic ulcers. Bandaging venous ulcers reduces edema and improves venous return. To achieve this, it is advisable to combine exercise and elevation of the leg during rest.

Compression therapy has advantages: it is comfortable for the patient, as they can continue with their work; it allows for spaced dressings and, therefore, reduces the cost of treatment. It is also effective, as it promotes rapid ulcer granulation. Before applying it, the existence of arterial compromise must always be ruled out. The fundamental basis of compression therapy is the bandage. Before starting it, it is essential to check for the existence of distal pulses.⁽²⁵⁾

The bandage should be applied when the venous pressure on the walls of the blood vessels is as low as possible, which happens when the patient is in the Trendelenburg position, which is undoubtedly the best position for applying it. It should not be used on patients sitting or with their legs elevated. In the presence of edema, keeping the patient in the Trendelenburg position is advisable until it subsides.⁽²⁶⁾

All bandaging should follow an ascending direction, starting at the base of the toes and ending after passing the popliteal fossa or reaching the inguinal region. It is considered that the bandage turns can be made circularly, the most advisable as it always maintains the same pressure, or in a herringbone fashion, which makes one turn ascending and another descending but does not meet the criterion of keeping pressure in the same direction. The optimal pressure, which is also usually well tolerated by the patient, is 35-40 mmHg, equivalent to five layers of standard 10 cm wide bandage. The pressure should decrease progressively as it rises to maintain the leg's physiological pumping.⁽²⁶⁾

In compression therapy, the first step is treating the ulcer using the previously mentioned cleaning and dressing methods. The bandaging, which can be done with different materials, is done immediately afterward.

Elastic stockings

These are made of a valuable and comfortable material, although the patient often has to get used to wearing them. In international commerce, four types are classified according to their compression capacity: light, moderate, vigorous, and extra-strong.⁽²⁷⁾

In general terms, the greater the force, the greater the effectiveness, but the worse the tolerance; for this reason, it is advisable to start with light or moderate compression stockings and gradually increase the compression. Likewise, full-length "panty" stockings provide more excellent protection than "stockings" or socks.⁽²⁷⁾

Like bandages, stockings provide more excellent compression at the ankle, 100 %, which progressively decreases to the thigh, 50 %, acting like the natural impulse exerted by the leg muscles. The stocking should be put on, like the bandage, after a long period of rest and when there is no edema; the best time is when getting up, and it is advisable to shower at night. In summer, they are uncomfortable, but this is also true when vascular insufficiency worsens, so it is advisable to keep using them, at least for a few hours. The useful life is about six months.⁽²⁷⁾

Bandages

The therapeutic pressure achieved with the use of bandages depends on the characteristics of each one and, above all, on their composition and elastic capacity. Rubber or polyurethane bandages retain their elasticity for longer than those made of stretchy fabric, which are generally made of crepe. They find it difficult to adjust and progressively lose their tension, meaning they must change frequently. The bandaging technique is fundamental.⁽²⁷⁾ However, some special types, such as Linton, Unna, and Duke boots, are considered.

Linton bandage

This is a classic form of bandaging that exerts pressure when the patient is standing and, to a lesser degree, when the patient is lying down. Before applying the bandage, it is advisable to protect the skin with an insulating cream such as water-based paste or petroleum jelly. The ulcerated area can be treated in the way

that is considered most appropriate, as this type of bandage is compatible with any local treatment.⁽²⁶⁾

The first dressing layer should be cotton; an elastic adhesive bandage should be applied circularly. Once the dressing is finished, it is advisable to check the coloration of the fingers, both when the patient is walking and when they are at rest, as well as to ask the patient if they feel too much tightness or tingling in the fingers; if so, it should be loosened until a good tolerance is found. The dressing should be changed weekly, although it can be done more frequently if required by the exudate from the ulcer. Low molecular weight heparin has been described as applicable in these post-thrombotic syndromes.⁽²⁷⁾

Unna boot

This is also a classic and valuable system in treating skin ulcers. It positively affects venous hypertension during orthostatism but not during rest.⁽²⁹⁾

Unna's boot results from the combination of a moist paste in contact with the wound and the external compression of the bandage itself. The paste used, although variable, can perfectly well be a water-based paste with which the entire bandage is impregnated and which should be adjusted perfectly, but without excessive compression. A zinc paste bandage is applied once the first layer has been used, creating a moist inner layer and a hard outer layer. It is advisable to check the bandage after 24 hours to ensure no signs of ischemia. The patient should be informed that they should go to the doctor's office if they feel pain, tingling, or any other noticeable symptom.⁽²⁹⁾

The dressing should be cared for as for any other injury and, depending on the amount of exudate, should be changed every three to fifteen days.

Duke Boot

This is a variation of the Unna Boot, but it has a hydrocolloid dressing to absorb the exudate.

Other researchers have used a foam rubber pad instead of the hydrocolloid pad mentioned above, and even the kind found in surgical scrub brushes can be used with good results. It should be emphasized that compression therapy should only be used for venous ulcers and is contraindicated for arterial ulcers.^(22,25)

Therefore, it should not be used when there is a decrease in pulses, if the oscillometry is decreased, or if the ankle systolic blood pressure is less than 80 mm Hg.⁽²⁵⁾

Mechanisms of the healing process

As soon as the loss of substance occurs, a series of complex mechanisms are set in motion, only partially known, and can be summarized in three phases: inflammation, proliferative, and maturation.⁽²³⁾

The first phase, which lasts approximately 72 hours, aims to plug the wound (clot formation) to facilitate its cleaning; platelets and various inflammatory cells, mainly granulocytes and macrophages, participate in it. Also, during this stage, a series of soluble mediators are released that initiate the healing process.⁽²³⁾

The primary purpose of the proliferative stage is to increase collagen and angiogenesis to form granulation tissue. The participation of endothelial cells is of great importance here. The maturation stage can last for years and is fundamentally based on collagen production and subsequent destruction.⁽²³⁾

In all these stages, keratinocytes participate, tending to migrate both from the edges and from the epithelial remains of the wound through their multiplication and maturation.

In the inflammatory phase, there is a high level of activity of resident cells (epithelial cells, fibroblasts, dendritic cells), as well as the production of different mediators that attract platelets, neutrophils, lymphocytes, and macrophages to the wound area and favor the phenomena of angiogenesis and, ultimately, the production of granulation tissue.⁽²³⁾

Polymorphonuclear neutrophils (PMNs) are the first inflammatory cells to reach the wound site. The PMNs remain for a short time if the wound does not become infected. Most of these cells are recorded between 24 and 48 hours. During this time, they act effectively, eliminating cellular detritus, foreign particles, and bacteria. The monocytes arrive at the wound shortly afterward, are activated, and transformed into macrophages.⁽³⁰⁾

Thus these cells, like the PMNs, also eliminate detritus, foreign particles, and bacteria, but they reach their maximum population peak later, at 48-72 hours; they remain for a more extended period, days to weeks, and participate in much more complex phases of the wound healing process, perpetuating the inflammatory process through the release of pro-inflammatory cytokines (interleukins 1, 1 β , 6), tumor necrosis factor (TNF), and stimulating the production of collagen by fibroblasts. Transforming growth factors β one and β 2, TGF- β 1 and TGF- β 2, pseudoinsulin growth factor (IGF) angiogenesis, vascular endothelial growth factor (VEGF), (TGF- β), and release growth factors that influence the epithelialization process. (TGF-IGF-1).^(29,30)

The ulcer releases factors within it, but we will only address those that may be of interest from the point of view of their therapeutic application:

1. Growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and nitric oxide (NO) are found in the exudate of ulcers and

are responsible for promoting chemotaxis, migration, stimulation, and cell proliferation;

2. Recombinant platelet-derived beta growth factor (PDGF- β) or becaplermin, PDGF, as well as epidermal growth factor for the treatment of diabetic foot, are accepted by the US Food and Drug Administration (FDA).^(23,30)

Phenomena associated with delayed healing of chronic ulcers

Antimicrobial resistance in bacteria does not appear as an isolated phenomenon but in a binomial relationship with the introduction of antimicrobials to combat infectious diseases, which has become a real international health problem. It is already known that more strains, species, and new mechanisms are involved in therapeutic resistance daily.⁽³¹⁾

Resistant bacteria can spread easily between people, particularly in environments where the high use of antimicrobials and the presence of debilitated patients hospitalized for long periods of time make dissemination a common phenomenon.

The growing increase in bacterial resistance abroad and in Cuba makes antimicrobial resistance surveillance a fundamental pillar for guiding patient management.⁽³¹⁾

In the treatment of various infectious diseases today, it is difficult to choose the appropriate empirical therapy. An up-to-date microbiological map will be essential, as it will serve as a basis for recommending the best alternative within the arsenal of options available today in the basic range of medicines.^(30,31)

Undoubtedly, the excessive and often empirical use of antimicrobials for treating different clinical situations has led to modifications in bacterial ecology, which can have fatal consequences for public health. Some countries have adopted measures to promote the appropriate use of antimicrobials. In Cuba, through pharmacovigilance,⁽³²⁾ strategies have been developed to encourage the rational prescription and use of drugs, emphasizing some therapeutic groups, among which antimicrobials are essential.

Recurrence of venous ulcers

Venous ulcer recurrence rates are considerably high despite significant advances in knowledge regarding prevention and treatment. This generates a not inconsiderable social and economic impact, making it necessary to establish the variables interfering with the correct evolution of this disease.

Health professionals sometimes lack the tools available to reduce the impact of the chronic and recurrent nature of venous ulcers.

Primary health care continues to be the determining factor; the context of the patient's home is where, through primary care, behaviors and care appropriate to the disease can be promoted in at-risk patients. To minimize the percentage of recurrences, the diagnosis and treatment of these lesions must be based on quality recommendations according to scientific evidence. The provision of non-standardized care, the incorrect monitoring of patients with a history of ulcers, and the failure to comply with the recommendations provided are the factors that explain why the recurrence rates are higher in some patients than in others.⁽²⁰⁾

Status of Ulcers in Latin America

A study in Uruguay found that of a total of 64 patients, 53,1 % were female, with an average age of 65,7 years. Their educational level was low, with 6,3 % being illiterate and 67,2 % having only reached primary level. Barely 1,6 % had reached, but not completed, tertiary level. In 70,3 % of cases, the etiology of the ulcer was venous, and it is worth noting that 57,8 % of them had been present for more than two years. During the follow-up period, 18,8 % of the patients were discharged, 60,9 % continued treatment, and 20,3 % abandoned it.⁽³³⁾

In Uruguay, there are no data regarding the magnitude of chronic ulcers. However, it has an aging population, which is usually affected by this lesion. According to data from the National Institute of Statistics and Census, those over 65 represent 13,6 % of the 3,344,938 inhabitants that this organization projected for the year 2009, so it can be inferred that a large number of Uruguayans are affected by ulcers in their lower limbs. 938 inhabitants that this organization projected for the year 2009, from which it can be inferred that a large number of Uruguayans are affected by ulcers on their lower limbs.

The results of two Brazilian studies indicate that the rates are higher than in the general population. The first obtained a rate of 3,6 % (2,3 % in men and 4 % in women), and the second, 3,2 % in men and 3,9 % in women. The authors also state venous ulcers are more common in older people, especially those between 65 and 70. The ratio between older women and men is three to one, with longevity being the predominant factor in women, since below the age of 40, the ratio is the same for both sexes.⁽³³⁾

Status of Ulcers in Europe

The objective of the study carried out in Spain in 2006, called DETECT-IVC, was to verify the high prevalence data of chronic venous insufficiency (CVI) obtained in the DETECT-IVC 2000 investigation due to the close relationship that this event shows with the development of post-thrombotic ulcers. For this, a cross-sectional

study was carried out, in which all subjects who attended the clinics for any reason were surveyed, and it turned out that 71 % of the cases had some symptom of CVI, 62 % had some sign, and 2 % had ulcers. Another study indicated that ulceration of the lower limbs affects 1 % of the adult population and 3,6 % of those over 65, tends to be recurrent, and its annual cost is estimated at around 400 million pounds (about 588 million euros).⁽³⁴⁾

In Germany, the most recent estimates indicate that 1,5 million people suffer from post-phlebotic ulcers. The costs derived from their treatment are around 1,54 million euros per year. In this country, studies that examine the epidemiology of ulcers found an incidence of ulcers in the lower extremities of 2 % in women and 3 % in men.

Studies in London identified 113 patients in a population of 252 000, with a crude prevalence of 0,45/1000 (95 % CI 0,37-0,54/1000): 0,34/1000 in men, 0,54/1000 in women. The proportions were very dependent on age, increasing to 8,29/1000 (men) and 8,06/1000 (women) in those over 85. The response was seen in 62/113 (55 %) who had an ulcer less than 1 year old. Complex causes were present in 48 (35 %) and were associated with comorbidities such as diabetes (35 %), lymphedema (42 %) and rheumatoid arthritis (26 %).⁽³⁵⁾

Epidemiology and studies aimed at specifying the clinical use of platelet preparations in the United States of America

Leg ulcers are caused by venous reflux disorders or obstruction. Between 1,5 and 3,0/1000 people have active leg ulcers. The prevalence increases with age to approximately 20/1000 in people over 80 in the United States.⁽³⁶⁾

Another example is the study in Michigan in 2005, where the prevalence of CVI in females varied between 1 and 40 % and in males between 1 and 17 %. This same study detected that the most relevant risk factors for this disease were advanced age, family history, and risky professions. Other research assesses CVI as the most frequent vascular disease, which in many cases leads to leg ulcers and is five times more frequent in women.⁽³⁶⁾

In recent years, the Tissue Engineering Laboratory group at Harvard University has focused on conducting in vitro analyses of the concentrations of the different CFs in PRP and its platelet-free supernatant to determine the CF load, its plasma levels, the relative distribution between the intra- and extracellular compartments in the sonicated sample and its redistribution after processing. The platelets' ability to release these factors was determined by quantifying their plasma concentration before and after activation.⁽²³⁾

The experimental model used was a model of eight-week-old male Lep/r-db/db homozygous diabetic mice, type C57BL/KsJ-Leprdb, for each experimental group, in which a 1x1cm wound was made in the skin and panniculus carnosus. The animals were randomly assigned to one of the two groups, and a single dose of one of the two preparations studied was applied to the wound. It was demonstrated that the frozen and dehydrated platelet preparations are adequate in the in vivo and in vitro stimulation of angiogenesis, re-epithelialization, and secondary wound closure, and maintain a sufficient concentration of platelet growth factors for up to 5 days after the established expiry date, which opened up the possibility of a reform in the standards for processing and buffering platelet preparations and a more efficient use of these blood components.⁽³⁰⁾

Current status in Cuba

In Cuba, the first epidemiological studies on ulcers were carried out in the 1970s, and these results have not yet been updated. The prevalence in men was 5,9 per 100 patients; in women, it was 11,4 per 100 patients (CI: 9,4-13,4; 95 %). In general, for this disease, adjusted for age and sex, it was 9,9 per 100 patients (CI: 7,9-11,9; 95 %). The increase in this figure was due to the prevalence observed in women. The estimated overall incidence was 1 % (CI: 0,2 %; 95 %).⁽³⁷⁾

Post-phlebotic ulcers are the most frequent complication and are disruptive and resistant to conventional treatments. They are caused by venous stasis, although they are preceded by other processes, such as dermatitis and cellulitis, as a result of trauma or an infectious outbreak.

This disease causes dysfunction in work activity. It has been pointed out that the family doctor and nurse play a fundamental role in the evolution of these patients, who together with the specialists, must deal with risk factors, improve the general condition of the patient as much as possible, treat the pain, rest the affected leg, avoid swinging the limb in bed as much as possible to prevent edema, protect the ulcer from the external environment (avoiding compression bandages and sticking plaster on the skin); raise the head of the bed by approximately 15 degrees, help the patient to give up smoking, administer the indicated medication, insist on postural measures.

Platelets, their discovery, and functions

Platelets were the last of the three formed elements of blood to be discovered, their identification being attributed to the French doctor Alfred Donne in 1842. The German anatomist Max Schultze confirmed the existence of these elements and was the first to describe them. Years later, George Hayem, in 1878, and Giulio

Bizzorero, in 1882, provided more information. Bizzorero called these new corpuscles “piastre,” small plates, which were later called “plaquettes” in French, “platelets” in English, and consequently, platelets in Spanish.^(23,30)

Platelets were described as “spherules” smaller than red blood cells, which sometimes appeared as aggregates and could participate in forming fibrous material; furthermore, it was shown that these structures were anucleated. The continuation of his studies provided valuable information on platelet involvement in the blood coagulation process.⁽²³⁾

Platelets as a source of growth factors

Platelets are viable fragments that are incorporated into every traumatic or surgical wound. Depending on their characteristics and therapeutic possibilities, they have been used for different purposes.

Understanding the function of platelets has led to developing a strategy to initiate tissue regeneration at a high level. The clinical use of PC or platelet-rich plasma (PRP) has shown a doubling of the speed of bone formation and a 20 % increase in the density of bone grafts.

Platelets contain multiple CFs, including PDGF, PDGF- β , IGF, and EGF. Other observed factors include epidermal growth factor (EGF) and hepatocyte growth factor.⁽³⁸⁾

The pharmaceutical industry promoted the development of PDGF-based products, which were approved in 1997. It should be noted that when using the so-called platelet patch, or platelet clot, high concentrations of PDGF, TGF B, and VEGF are applied, thus increasing adhesiveness and enhancing the effect.⁽³⁸⁾

However, PRP does not only contain platelets but also plasma with fibrin and other CFs that influence healing. Fibrin acts as a provisional scaffold for cell migration and differentiation of stem and primary cells and functions as a biological glue.⁽³⁹⁾

There are several reasons for the current interest in using PCs to heal defects, bone consolidation, and osseointegration.⁽³⁸⁾

First, the body’s natural and immediate response to damaged tissue is accumulating many activated platelets at the injured site. The activated platelets interact within the coagulation cascade at various levels, and a clot forms quickly.

Second, the α granules contained in the platelets release FC and cytokines. These proteins, which include PDGF, TGF, VEGF, and EGF, attract macrophages, mesenchymal cells, osteoblasts, and cells responsible for removing necrotic tissue. The released proteins act as chemotactic, morphogenetic, and mitogenic agents. The secretion of pre-synthesized proteins occurs within the first 10 minutes of platelet activation, and more than 95 % are secreted within the first hour. Platelets continue to secrete these proteins during their half-life of five to 10 days and up to 21 days after being extracted for donation. Therefore, a supraphysiological dose of activated platelets can theoretically accelerate the healing process, thus inhibiting bacterial growth.⁽³⁹⁾

Third: Technologically, it is available by taking a 60 mL volume of venous blood from the patient and processing the PRP as another alternative.

The use of different elements whose structure is related to CF, whether these are of natural origin or the result of gene recombination, has modified the treatment of chronic lesions, both in orthopedic surgery and in maxillofacial surgery and the closure of post-phlebotic ulcerative lesions.⁽³⁰⁾

As already mentioned, the usefulness of platelets in other specialties is now a proven fact.

PRP has beneficial effects in joint surgeries, in which it is necessary to fill a bone defect at the time of arthroplasty or in complicated fractures that fail to heal.⁽⁴⁰⁾

It is important to remember the principles of basic surgery, such as biomechanical stability, tissue coverage, preserving vascularization, eradicating infection, and an ideal environment for bone and ulcer repair. The possibility of carrying out the treatment in the operating theatre, consulting room, or patient’s room allows for its wide use.

Biological activity of the main platelet growth factors

The first reference to bioactive substances characterized as growth factors was the so-called (EGF) made by the same group of scientists who discovered the so-called nerve growth factor (NGF).⁽⁴¹⁾

These substances can stimulate mitosis, proliferation (healing), and angiogenesis and promote chemotaxis, among other properties.⁽⁴²⁾

The so-called cellular communication results from research into these factors, which constituted a breakthrough in understanding this process.⁽⁴²⁾

Knighton’s work based on a randomized study was the first to demonstrate the beneficial effects of the so-called Platelet-Derived Growth Factor (PDGF) in the treatment of chronic wounds.⁽⁴²⁾

Table 2 summarizes the impact, biological action, or both properties of each of the CFs, which can, in advance, justify the reason for the healing and the reproductive capacity of the coagulation stages of these factors.

Table 2. Activity of bioactive molecules⁽⁴⁰⁾

Molecular bioactivity	Biological activity
Platelet-derived growth factor (PDGF)	- Potent mitogen for fibroblasts, arterial smooth muscle cells, chondrocytes, epithelial cells and endothelial cells
Vascular endothelial growth factor (VEGF)	- Potent chemotactic effect for hematopoietic and mesenchymal cells,
Transforming growth factor beta (TGF- β)	- Stimulates chemotaxis and activation of muscle macrophages and fibroblasts
Insulin-like growth factor types I and II (IGF-I and IGF-II)	- Activates transforming growth factor b to stimulate macrophages and neutrophils
Acid and basic fibroblast growth factor (ABGF and BFGF)	- Synthesis of type I collagen
Epidermal growth factor (EGF)	- Angiogenesis (indirectly)

Source: Taken from Fernández Delgado N, et al. 2012

Regenerative medicine in Cuba. Current therapeutic alternative

New minimally invasive techniques have recently been developed to obtain biomaterials used in regenerative dental therapies based on tissue engineering concepts. Recently, in some oral and maxillofacial surgery, periodontics, and endodontics procedures, techniques utilize blood derivatives known as platelet concentrates, which are applied alone or in combination with other materials to enhance their effect.⁽⁴³⁾

Platelet-rich fibrin (PRF) is a platelet concentrate defined as an autologous biomaterial free of anticoagulants and external chemicals.⁽⁷⁾ It is obtained in a single process of centrifuging peripheral blood, in which a fibrin network is formed with a high concentration of platelets and leukocytes, which secrete key biomolecules in tissue repair and/or regeneration.⁽⁸⁾ Although some molecular mechanisms have been identified that are activated when PRF comes into contact with tissues, structural aspects associated with the collection process are not completely clear.⁽⁴³⁾

The technique for obtaining PRF is based on the migration of blood components by gravitational force, which generates variability in the structure of the PRF when the same centrifugation protocol is performed with different equipment.⁽¹⁰⁾ As with platelet-rich plasma (PRP), since the development of PRF, different centrifugation protocols have been reported in the literature, mainly focused on modifying the time (from 8 to 12 minutes) and the speed (from 2500 to 3200 rpm) which generates different results in the concentrates and therefore variable clinical results, possibly associated with structural changes.⁽⁴⁴⁾

The alteration of the fibrin network and the changes in the amount of platelets contained in PRF can affect the in situ results because there is a correlation between platelet count in the PRF and the expression of growth factors.⁽⁴⁴⁾ This makes it necessary to standardize the collection protocol according to the equipment available and the biomedical applications to identify the patterns of cell distribution within the fibrin network and thus guarantee the quality of the biomaterial so that it can be applied efficiently in the different clinical dental needs with success and less variability in the clinical results.

The Hospital General Comandante Pinares is currently offering consultations in Regenerative Medicine as a new service to the population. A multidisciplinary team staffs it and treats mainly orthopedic, ophthalmological, coloproctological, and geological conditions. After 20 years of work, the scientific community is now in a position to report that the latest findings on the methodological aspects of post-phlebotic ulcers have made it possible, based on the evidence, to review the possibility of achieving tissue regeneration through platelet- and leukocyte-rich fibrin, using an autologous biomaterial, and even the simple and rapid methods for obtaining it.

CONCLUSIONS

The current state of knowledge of the main aspects related to post-phlebotic ulcers from a pedagogical-scientific-technological approach suggests the design of projects that lead to research into this disease.

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The authors declare that there is no conflict of interest.

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