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Clinical Research

Influence of Aspirin Therapy in the Ulcer Associated With Chronic Venous Insufficiency

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Background: To determine the effect of aspirin on ulcer healing rate in patients with chronic venous insufficiency, and to establish prognostic factors that influence ulcer evolution.
Methods: Between 2001 and 2005, 78 patients with ulcerated lesions of diameter >2 cm and associated with chronic venous insufficiency were evaluated in our hospital. Of these, 51 patients (22 men, 29 women) with mean age of 60 years (range: 36–86) were included in a prospective randomized trial with a parallel control group. The treatment group received 300 mg of aspirin and the control group received no drug treatment; in both groups, healing was associated with standard compression therapy. During follow-up, held weekly in a blinded fashion, there was ulcer healing as well as cases of recurrence. Results were analyzed by intention-to-treat approach. Cure rate was estimated using Kaplan–Meir survival analysis, and the influence of prognostic factors was analyzed by applying the Cox proportional hazards model.
Results: In the presence of gradual compression therapy, healing occurred more rapidly in patients receiving aspirin versus the control subjects (12 weeks in the treated group vs. 22 weeks in the control group), with a 46% reduction in healing time. The main prognostic factor was estimated initial area of injury ($P = 0.032$). Age, sex, systemic therapy, and infection showed little relevance to evolution.
Conclusions: The administration of aspirin daily dose of 300 mg shortens the healing time of ulcerated lesions in the chronic venous insufficiency (CVI). The main prognostic factor for healing of venous ulcerated lesions is the initial surface area of the ulcer.

INTRODUCTION

Venous ulcers are a common complication and a therapeutic challenge for physicians who treat them. The current sensitivity against this highly prevalent health problem has prompted research into the pathophysiology and treatment of venous disease.

The deterioration of the venous valves, the remodeling of the wall, and microcirculatory dysfunction are related not only to venous hypertension but also with the existence of a cascade of biochemical events that contribute to the progression of chronic venous insufficiency (CVI).[1] Of all the proposed mechanisms that link venous hypertension to changes in the macro- and microcirculation, currently, the most accepted is the leukocyte–endothelium interaction, according to which leukocytes (mainly monocytes and macrophages) infiltrate the valves and the vein wall causing valvular destruction and remodeling of varicose vein. The accumulation of leukocytes in the microcirculation is due to their adherence to the endothelium and migration through postcapillary venules.[2] Still, genetic and molecular determinants of the development of varicose veins and chronic venous disease are currently unknown, and knowledge is essential to improve therapeutic interventions and disease prevention.

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So far, the treatment of venous ulcer has been unsatisfactory. Compression therapy is effective in healing, but patients return for treatment in a few months. Surgical treatment offers a possible solution only for patients in whom superficial venous reflux is the main problem, whereas valve reconstruction of the deep veins is an option only for very few patients.

The interest in understanding the pathophysiological mechanisms of chronic venous disease has helped establish drug targets for improving adjuvant treatment. Assuming that leukocyte activation is an important mechanism in the perpetuation of venous insufficiency and platelets, reflecting the systemic inflammatory response may be relevant in the genesis of venous disease, and drugs inhibiting leukocyte activation and platelet function should be considered in the treatment of this disease to achieve better results.

The objectives of our study are to determine the effect of acetylsalicylic acid (ASA) on the rate of healing of venous ulcers in patients with CVI, and to establish prognostic factors that influence healing of venous ulcers.

MATERIAL AND METHODS

Design

The influence of ASA on ulcer healing was determined by using a prospective, randomized, parallel group, double-blind control. The research project and informed consent were approved by the Local Committee for Clinical Trials and Ethics Committee of our hospital. We used a total randomization using random numbers selected by a computer. Patients were first randomized at the time of inclusion by an independent researcher involved in the healing process of injuries and the analysis of results.

Patients

Between December 2001 and September 2005, 78 patients with ulcerated venous lesions of diameter >2 cm were evaluated in the Department of Angiology and Vascular Surgery of University Hospital of Valladolid (Spain). Fifty-one subjects who were included in the study were randomized into two groups: group treated with ASA ($n = 23$) and untreated control group ($n = 28$). All of them were given informed consent and were provided explanations, verbally and in writing, regarding what the study involved and the risks in it.

Inclusion and Exclusion Criteria

Patients with ulcerated lesions of entirely venous origin and a diameter of ≥ 2 cm, with ankle–brachial index of >0.9, and no contraindication for the administration of ASA were included in the study.

Patients with diabetes mellitus, rheumatoid arthritis, peripheral arterial disease (ankle–brachial index: <0.9), neurological diseases, and previous or concomitant therapy involving aspirin, anticoagulants, or nonsteroidal anti-inflammatory drugs were excluded.

Intervention

All patients were treated at the outpatient clinics of our hospital and were randomized into two groups. One group received 300 mg of aspirin daily (treated group) and the other group received no drug treatment (control group). In both groups, compressive treatment and healing of venous ulcers locally were conducted evenly for all patients. The venous ulcer treatment was performed by correcting the general factors that inhibit or delay the ulcer healing, including antibiotic treatment when infection is present in the ulcerated lesion, and by the local healing of the lesion, using the same systemic treatment approach for all patients, which consisted of cleaning, debridement, and application of a hydrocolloid dressing. The cleaning was done in an aseptic environment, with a gentle washing of the ulcer and surrounding skin with saline. In the case of ulcer epithelialization phase, the bottom of the lesion was cured with special care, as aggressive cure can damage granulation tissue and weaken the newly formed epithelium. Later, in the presence of devitalized tissue, surgical debridement was performed and then a hydrocolloid dressing (carboxycellulose) was applied, which absorbed water and exudate, thus maintaining and stimulating granulation in a wet environment. We did not use topical agents such as corticosteroids or antiseptics. After the healing of the lesion, a bandage was applied to all patients, which consisted of a compression system of two layers, where the first layer provided cushioning and allowed shaping the morphology of the lower extremities and bony prominences and the second layer was elastic and exerted continuous and decreasing pressure at the ankle (40 mm Hg), incorporating a range control. This system adapts to the reduction of edema and ensures proper compression for a week without reapplication.

The venous system was studied by performing a Doppler ultrasonography to determine the permeability of the deep venous system and superficial and/or deep venous system incompetence. The study of the arterial system was performed by measuring the ankle–brachial index using a continuous Doppler. Other data that were collected as part of

patient history were age, sex, performance status, degree of collaboration, activity, mobility, presence of incontinence, hydration, presence of comorbidity (diabetes mellitus, hypertension, Alzheimer's disease or dementia, chronic arterial insufficiency, chronic obstructive pulmonary disease), and concomitant drug therapies, as outlined in the enclosed form on clinical and laboratory data (Annex I).

Determinations

We studied biochemical and hematometra levels to exclude systemic disorders that may adversely affect the healing of ulcers, and these were corrected when necessary. Data regarding the number of ulcerated lesions, location, time of evolution, size and shape of lesions, as well as the characteristics of the ulcer (periulceral skin condition, degree of necrosis, slough, granulation and epithelialization, signs of infection, and microbiological culture collection) were collected at each visit, as described in the enclosed form on venous ulcer characteristics (Annex II). The ulcer size was determined by a method of planimetry and for patients with multiple injuries, was monitored over all as the reference lesion. The staging of ulcers was conducted using the National Pressure Ulcer classification system,[3] which provides four grades:

- Grade I: The skin is intact but erythematous.
- Grade II: There is a partial loss of skin thickness with involvement of the epidermis and dermis.
- Grade III: There is a complete loss of skin thickness and subcutaneous tissue is affected.
- Grade IV: When the lesion is deep and affects the muscle and bone.

Monitoring

Ulcerated lesions were monitored weekly to detect evolutionary changes of the lesion. The main warning signs were the onset of pain, odor, and new areas of necrosis or slough. In such situations, the ulcer was reassessed from a general and local (to assess primary etiologies or the presence of local infection or other reasons for the decline) standpoint. After complete epithelialization of the lesion, the patient continued with compression therapy and periodic review, which lasted until the present time. All patients included in the study completed the treatment and follow-up appropriately.

Statistical Analysis

To evaluate the influence of ASA on the healing of venous ulcerated lesions, the calculation of necessary sample size was first performed. To do this, we set a 5% α risk ($z_\alpha = 1.645$, for unilateral assumption), power (1-β) of the study was 90% ($z_\beta = 1.282$), an expected difference of 45% between the two treatments (P1−P2) was considered, and the following formula was applied for calculating sample size for comparison of two proportions:

$$n = \frac{\left[Z_\alpha * \sqrt{2p(1-p)} + Z_\beta * \sqrt{p_1(1-p_1) + p_2(1-p_2)}\right]^2}{(p_1 - p_2)}$$

Based on these data, it was concluded that 19 patients were needed in each group. After that, we applied a correction factor of 10% for estimated losses that occur in all follow-up studies that would have a sample size of 42 patients (21 in each group).

Then we studied the homogeneity of both groups with χ^2 test for qualitative variables and Student *t* test for independent groups for quantitative variables following a normal distribution tested by the Kolmogorov−Smirnov−Lilliefors test. In the case of quantitative variables that did not follow a normal distribution (study period and surface area of the ulcerated lesion), nonparametric Mann−Whitney test was applied.

The rate of healing of venous ulcers in both groups was subsequently estimated by analysis of the survival function and Kaplan−Meier comparison was made through the log-rank method, considering *P* value of <0.05 to be significant.

Results were analyzed according to the intention-to-treat approach. The identification of prognostic factors of healing was performed using binary logistic regression analysis (forward stepwise method). The presence or absence of healing was considered as the dependent variable in the model (*y*), whereas the administration of antiplatelet therapy was considered as an independent variable (*x*). Covariates entered into the regression model were age, gender, lesion location, duration until initiation of ulcer treatment, stage, initial surface area of the ulcer, and the existence of signs of infection. For statistical analysis, we used SPSS 15.0 licensed to the University of Valladolid (SPSS version 15.0, SPSS Inc., Chicago, IL).

RESULTS

Of the 78 patients presenting with ulcer of venous origin between December 2001 and September 2005 from our Department of Angiology and Vascular Surgery, University Hospital of Valladolid, 51 patients (22 males and 29 females) with a mean age of 60 years (range: 36−86) were included in

Table I. Characteristics of the subjects in the clinical phase of the study

Variables	Control	Aspirin	Total	*P*
Age	58.59 (SD: 16.55)	60.50 (SD: 12.07)		0.65[a]
Sex				
Male	9	13	22	0.08[b]
Female	19	10	29	
Comorbidity				
None	10	9	19	0.052[b]
HTA	6	6	12	
PVT	8	6	14	
PTV + HTA	3	2	5	
CRI	1	0	1	
Total	28	23	51	
Pretreatment				
None	20	10	30	0.23[b]
Anxiolytics	0	1	1	
ANTIHTA	6	7	13	
AB	1	1	2	
ANTIHTA + pentoxifylline	1	0	1	
AB + diuretic	1	0	1	
Dipyridamole	2	0	2	
AB + ANTIHTA	0	1	1	
Total	31	20	51	
Duration of study (to complete epithelialization) (wk)	16.5	12.4		0.07[c]

HTA, arterial hypertension; CRI, chronic renal insufficiency; ANTIHTA, antihypertensive; AB, antibiotics; SD, standard deviation.
[a]Student *t* test.
[b]χ^2 test.
[c]Mann–Whitney test.

the study. Twenty-seven patients were excluded for the following reasons: presence of diabetes mellitus ($n = 3$), rheumatoid arthritis ($n = 1$), peripheral arterial disease (ankle–brachial index: <0.9) ($n = 9$), or neurological disease ($n = 1$), or pretreatment with aspirin, oral anticoagulants, or nonsteroidal anti-inflammatory drugs ($n = 13$). The 51 patients included in the study were randomized into two groups: group treated with ASA ($n = 23$, 15 patients were $C6sEpAs_{(2)Pr}$ and 8 patients were $C6sEsAp_{(13)}$ Pr) and untreated control group ($n = 28$, 17 patients were $C6sEpAs_{(2)Pr}$ and 11 patients were $C6sEsAp_{(13)}$ Pr). Table I shows the characteristics of study subjects, and Table II shows the characteristics of ulcerated lesions.

The groups showed no statistically significant differences regarding age, sex, comorbidity, previous medical treatment, length of study, lesion location, duration of ulcer before the study (although the duration of ulcer before treatment was higher in the control group than the group treated for durations of 6–12 months and >12 months), initial area of the ulcer, stage of the lesion, and signs of infection, showing homogeneity against these variables. Of the 51 patients, 28 (54.9%) had multiple ulcers compared with 23 (45.1%) presenting with a single lesion in the lower extremities, without incurring a statistical difference between groups. In all, 74.5% of patients had ulcerated lesion classification grade III National Pressure Ulcer, and 82.35% of patients (20 in the treated group and 22 in the control group) had venous ulcers with signs of infection at first visit. The organism most frequently isolated in the microbiological studies was *Staphylococcus aureus* (41.12%), followed by *Pseudomonas aeruginosa* (12.14%), *Corynebacterium striatum* (5.6%), and *Enterobacter cloacae* (5.6%), with similar distribution in both groups ($P = 0.126$) (Fig. 1). The average length of study to complete epithelialization of the lesion was 14.45 weeks ($range_{min-max}$: 1–71 weeks).

To determine the rate of healing of venous ulcers in both groups, Kaplan–Meier survival analysis was performed, as illustrated in Figure 2. Complete re-epithelialization of the ulcerated lesions occurred in 21 of the 28 patients in the control group (0.73%) and 17 of the 23 patients in the treated group (0.75%), showing no statistically significant differences between both groups, but the healing period was shorter in patients treated with ASA (log-rank test $\chi^2_1 = 3.90$, $P = 0.04$, odds ratio = 0.93, 95% confidence interval = 0.25–3.5), which

Table II. Characteristics of venous ulcers in the clinical phase of the study

Variables	Control	Aspirin	Total	*P*
Location				
Internal	19	14	33	0.489[a]
External	6	5	11	
Anterior	2	4	6	
Back	1	0	1	
Evolution				
<1 month	1	2	3	0.247[a]
1−3 months	10	5	15	
3−6 months	5	6	11	
6−12 months	5	2	7	
>12 months	10	5	15	
Phase				
II	1	2	3	0.95[a]
III	21	17	38	
IV	5	5	10	
Signs of infection				
No	7	2	9	0.094[a]
Yes	22	20	42	
Surface (cm^2)	24.87	25.15		0.944[b]

[a]χ^2 test.
[b]Mann−Whitney test.

was statistically significant. The average time of venous ulcer healing was 12 weeks in the treated group and 22 weeks in the control group; the cure duration being 50% shorter in patients receiving antiplatelet therapy than control subjects (7 vs. 12 weeks, respectively). This represents a 46% reduction in healing time of injuries. The percentage of subjects lost to follow-up in the study was 7.14% in the untreated group (two patients) and 9.5% in the treated group (two patients). In two cases, hospital admissions prevented study continuation, whereas patients' decision to continue treatment in a health facility nearest to them was responsible for discontinuation in two other cases.

The patients were followed from the time the ulcer re-epithelialized fully until May 2008 (average of 42 months; range: 24−60 months). During this period, 33.33% of patients in the untreated group and 25% of patients in the ASA-treated group relapsed, no statistically significant difference was observed ($P = 0.74$) (Fig. 3). The average time of injury recurrence was 16.33 days (standard deviation: 7.5) in the untreated group and 39 days (standard deviation 6.0) in the treated group, and this was statistically significant ($P = 0.007$) (Table III).

After analyzing the main prognostic factors for venous ulcer healing, the only variable that influenced all factors analyzed in the rate of venous ulcer healing was the initial area of injury ($P = 0.032$, 95% confidence interval = 0.882−0.994) (Table IV), which showed a power rating of 83.7% ($\chi_1^2 = 6.69$, $P = 0.01$), a value that was acceptable when it exceeded the threshold of 75%.

DISCUSSION

The venous ulcer is the result of the failure of proper management of CVI, which progresses to its most severe degrees. Initially, the main treatment for venous ulcers is conservative, based on the correction of venous hypertension with compression therapy and locally curing the injury. The investigation of the pathophysiologic mechanisms of venous ulcer is considered of great interest because of the possibility of finding drug targets that aid in improving the treatment of venous ulcers and preventing recurrence. In this study, we demonstrated that treatment with aspirin can be effective in healing ulcerated lesions of venous origin when used as an aid to local comprehensive treatment and related therapies.

Compression therapy not only reduces the volume of the limb to the smallest diameter possible, but also involves the patient in the active care of the limb. This was demonstrated by Cullum et al.,[4] who conducted a comprehensive literature review that noted ankle pressure of between 35 and 45 mm Hg to be the most effective and to result in more effective multilayer systems. In our study, we chose to use a system consisting of a two-layer bandage because its effectiveness has been clearly established,[5−7] and it provides a compression of 40 mm Hg at the ankle, which is the level of external compression more effective in the treatment of venous ulcer.[8]

The aim of topical treatment is to achieve the best possible conditions that can cause scarring of the lesion. It has been experimentally shown that wound healing is accelerated in a wet environment, as it promotes the preservation of cellular integrity and the implementation of the physiological mechanisms of tissue regeneration. A systematic review in the Cochrane database recommends that for the majority of venous ulcers, a simple nonadherent absorbent dressing provides insufficient protection to the ulcer under compression system[4]; therefore, we decided to use hydrocolloid dressings, which favor granulation and epithelialization processes.[9]

As in most open wounds, ulcerated lesions are rapidly colonized by pathogenic or nonpathogenic bacteria; however, interestingly, up to 15% of venous ulcers present a microbiological sterility in crops.[10] In our study, we identified that up to 17% of ulcers were free of bacteria. The bacterial flora that affects ulcers is usually uniform but often changes during lesion evolution, as we objectify

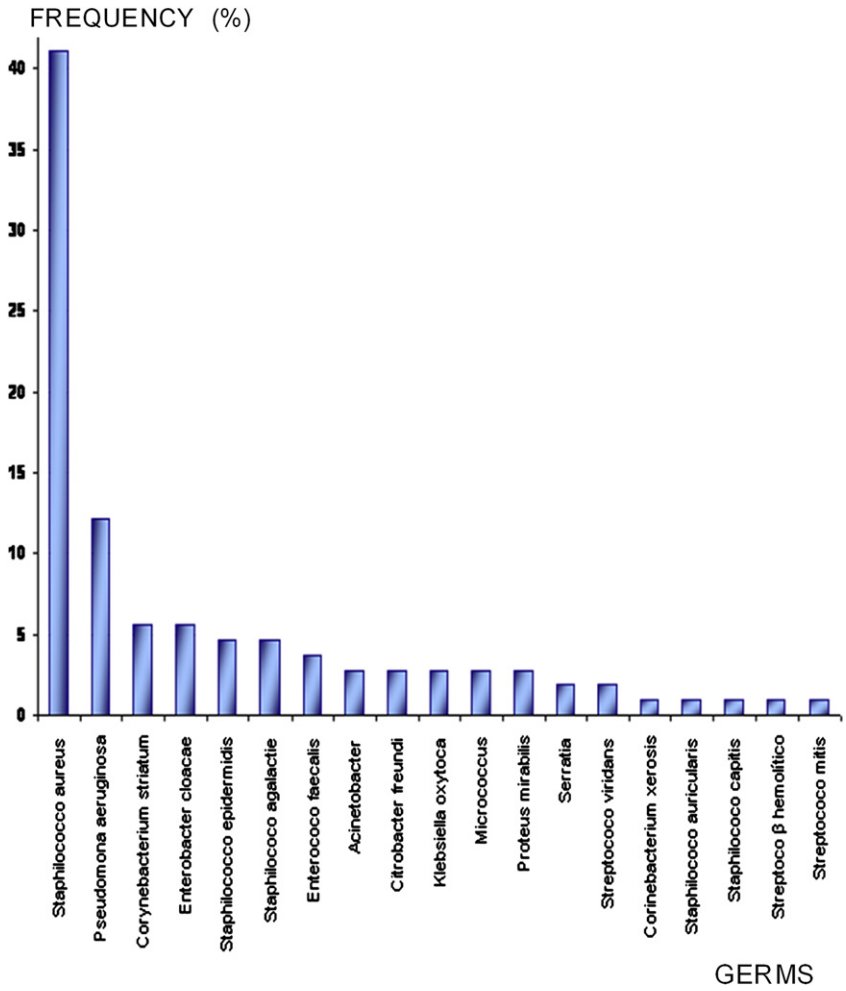

Fig. 1. Frequency distribution of bacteria isolated from the ulcerated lesions.

throughout the study. As described by other authors,[10] the organisms most commonly isolated in our study were *Staphylococcus aureus*, followed by *Pseudomonas aeruginosa, Corynebacterium striatum*, and *Enterobacter cloacae*. These aerobic bacteria are usually located in the center of the injuries, unlike other staphylococci, streptococci (*Streptococcus* β-*hemolyticus*), and enterococci, which are usually located on the periphery of ulcers.[10]

Recent studies show that the hemodynamic changes resulting from venous hypertension induce activation of leukocytes, endothelial cells, and platelets that participate in the marginalization, adhesion, and leukocyte activation.[11] In addition, several cytokines, free radicals, and proteolytic enzymes are synthesized and released by activated leukocytes to restructure the vessel wall but ultimately lead to the aggravation of venous disease.[12]

A number of drugs capable of modifying leukocyte activation have been evaluated in patients with venous ulceration with different results. These include studies with pentoxifylline, prostaglandin E_1, prostacyclin analogs, flavonoids, and ASA. The most rigorous study done with pentoxifylline has been reported by Colgan et al.,[13] in which pentoxifylline showed a benefit in healing of venous ulcers, although the work was carried out with small lesions in young patients without the presence of deep vein thrombosis, which, in itself, indicates a favorable prognosis of injuries. Rudofsky conducted a study of venous ulcers where administration of prostaglandin E_1 resulted in an improvement in edema, symptoms, and healing of the lesion, but only 8 of 20 patients in the treated group and 2 of the 22 patients in the control group were able to complete the study.[14] Iloprost is a synthetic analog of prostacyclin that has been used successfully in the treatment of arterial and venous ulcers in diabetic patients; however, the results of a previous study were disappointing when iloprost was applied topically.[15] The micronized purified flavonoid fraction has important effects on leukocyte activation.[16]

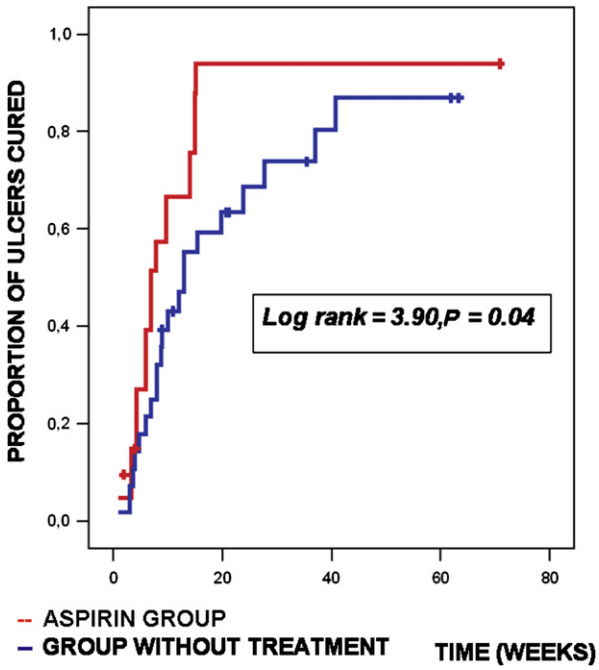

Fig. 2. Survival analysis of the rate of healing of venous ulcers during the study.

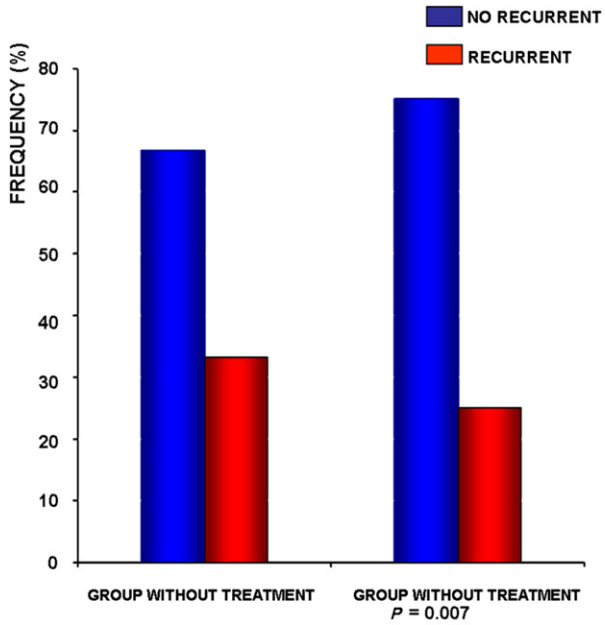

Fig. 3. Distribution of ulcer recurrence rate in the group treated with aspirin and the untreated group.

Its beneficial effects have been demonstrated in three multicenter, randomized, control-group trials,[17–19] and when associated with compression and local treatment of the ulcer, a 17% reduction in healing time was obtained.[19]

The use of aspirin for CVI was first reported by Layton et al.[20] in 1994. This author studied the effect of aspirin on the rate of ulcer healing in a randomized placebo control group. The major weaknesses of his study were the inadequate number of patients and the fact that the ulcer-free time could not be established, such that no valid conclusions could be drawn. Other studies have suggested the existence of alterations in coagulation (fibrinogen, factor VIII, von Willebrand antigen, and plasminogen activator inhibitor 1) in patients with CVI, which can be modified by the use of aspirin.[21] Since 1995, no further work has been published on the effectiveness of aspirin, despite the fact that this drug can block the inflammatory process and platelet aggregation underlying the pathophysiology of CVI. In our work, we reported that the group treated with ASA showed an acceleration in the healing process (12 weeks in the treated group vs. 22 weeks in the control group) with 46% reduction in cure time; the difference between the two groups was statistically significant ($P = 0.04$). Kaplan–Meier analysis was used to study the rate of venous ulcer healing in both groups, and the log-rank method was used for comparison of survival functions of both groups. Re-epithelialization of lesions occurred in 75% of patients in both groups, indicating that compression therapy was successful. When treatment of venous ulcers is associated with an adequate compression therapy, a cure rate as high as 60% to 80% in 6 months, according to the Base Review Cochrane,[8] or 93% in 5.3 months, according Mayberry et al.,[22] can be obtained The recurrence rate was lower in the group treated with ASA, but this difference was not significant; however, it showed statistically significant ulcer-free period, which was longer in the group treated with aspirin (16.33 ± 7.5 days in the control group vs. 39 ± 6 days in the treated group).

To determine the influence of prognostic factors in healing ulcerated lesions, we performed a regression analysis using Cox proportional hazards model. In our study, the only variable that significantly influenced the healing of venous injury was the initial surface area of venous ulcers; other variables such as age, history of deep vein thrombosis, and the presence of infection showed no influence. Several groups have studied the prognostic factors affecting wound healing of venous ulcers treated with compression therapy.[23,24] Stewart and Leaper[25] reported the relationship between ulcer area and duration. Franks et al.[26] identified three major factors that can delay the healing of an ulcer: the ulcer size, duration before treatment of the ulcer, and limb mobility. Kikta et al.[27] found under the ulcer area as a risk factor, whereas Colgan et al.[13] found no significant relationships. In none of these studies demonstrated the relationship with age which has been determined

Table III. Recurrence rate and average time of recurrence of venous ulcer in control group and the treated group

Groups	Ulcer recurrence (%)	Average time of recurrence ($P = 0.007$)
Control group	33.3	16.33 ± 7.5
Treatment group	25	39 ± 6

Table IV. Variables and covariables in the regression model with statistical significance

Variable	Coefficient	χ^2	*P*	Odds ratio
Constant	1.969	15.307	0	7.163
Initial area	−0.66	4.58	0.032	0.936

Variable	*P*
Constant	0
Initial area	0.032
Antiplatelet treatment	0.315
Age	0.937
Localization	0.663
Evolution	0.348
Phase	0.789
Infection	0.857

as independent prognostic factor for arterial and hypertension[28] although these pathologies associated with the CVI may worsen the prognosis of venous ulcers. Some authors have proposed the popliteal vein reflux as an independent risk factor,[29,30] whereas others such as Guest et al.[31] have suggested that it is an important factor in the delay of ulcer healing. The presence of bacterial contamination appears to have little significance in healing of the ulcer. We found no relation between the presence of infection at the initiation of treatment and healing of the same ulcerated lesion; however, we noted microbiological changes during the healing process of the injury, which coincides with views expressed by Ormiston et al.[32] It seems logical to recommend the identification of the initial area of the venous ulcer when comparing different therapeutic approaches. This determination must be made by planimetry, which is the correct method for measuring the lesion.[24] This prognostic factor ''initial lesion area'' allows us to identify patients in whom evolution can be worst, which can help us raise more adequate treatment in patients with poor prognosis. Unfortunately, recurrence of the ulcer is common[33,34] and many patients suffer multiple episodes of ulceration.[35] The primary method of preventative treatment involves providing compression of between 35 and 45 mm Hg at the ankle.[36] Greater the degree of compression that the patient can tolerate, lower is the incidence of recurrence.[37]

CONCLUSIONS

The healing of ulcers in CVI is accelerated by the administration of aspirin at doses of 300 mg daily as adjunctive therapy to local treatment and compression therapy.

The ulcer relapse rate was lower in patients treated with aspirin, and recurrence-free period of venous ulcers was longer in patients treated with aspirin. The main prognostic factor in the healing of venous ulcerated lesions was the initial surface area of the ulcer. The identification of prognostic factors should be carried out in all patients because it helps stratify the cure rate and guides our attitude regarding individuals with poor prognosis.

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Annex I. Clinical data sheet

Identification variables

Name
Age
Sex
Study start date
Center
Population

Initial patient assessment

General condition
☐ Good
☐ Weak
☐ Bad
☐ Very bad

Mental state
☐ Alert
☐ Apathetic
☐ Confused
☐ Stuporous

Activity
☐ Unassisted ambulation
☐ Assisted ambulation
☐ Wheelchair
☐ In bed

Mobility
☐ Total
☐ Slightly limited
☐ Very limited
☐ Motionless
Incontinence
☐ No
☐ Occasional
☐ Urinary
☐ Double
Hydration
☐ Normal
☐ Mild dehydration
☐ Severe dehydration
Associated pathology
☐ Diabetes mellitus
☐ Hypertension
☐ Alzheimer's/dementia
☐ Chronic arterial insufficiency
☐ Chronic venous insufficiency
☐ COPD
☐ Other
Pretreatment
☐ Anxiolytics
☐ Neuroleptics
☐ Hypnotics
☐ Immunosuppressive
☐ Corticosteroids
☐ Other

Annex II. Information document for venous ulcer

Description initial ulcer
Number of injuries
Locations
Ulcer no
Location
Etiology
☐ Pression
☐ Venous
☐ Arterial
☐ Mixed
☐ Other
Time of evolution
☐ Less than a month
☐ 1–3 months
☐ 3–6 months
☐ 6–12 moths
☐ >12 months.
Size of ulcer
☐ Length in cm
☐ Width in cm
☐ Surface in cm^2
Morphology
☐ Round
☐ Oval
☐ Irregular
☐ Other
Evolution of the ulcer

Date	Week 1	Week 2
Phase		
Surface		
Periulcer skin	☐ Normal ☐ Macerate ☐ Other	☐ Normal ☐ Macerate ☐ Other
Tissue type	Necrosis % Slough % Granulation % Epitheliali -zation %	Necrosis % Slough % Granulation % Epitheliali -zation %
Signs of infection	☐ No ☐ Yes	☐ No ☐ Yes
Culture	☐ No ☐ Yes	☐ No ☐ Yes
Antibiotic therapy	☐ No ☐ Yes	☐ No ☐ Yes