UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

PhD THESIS
ABSTRACT

PROGNOSTIC FACTORS IN VENOUS ULCER HEALING

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SUMMARY

KEY WORDS:

CHRONIC VENOUS DISEASE, VENOUS LEG ULCER, RISK FACTORS, HEALING

INTRODUCTION

The term chronic venous disease is used to describe a broad clinical spectrum caused by morphological and functional abnormalities of peripheral venous system and defines any long term morphological and functional alteration of venous system, manifested by signs and symptoms that require investigation and appropriate treatment.

Chronic venous disease clinical pattern includes a wide range of signs and symptoms from spider veins and varicose veins to leg edema and trophic and ulcerative skin changes.

Chronic venous disease is a widespread health problem and consume a lot of health care systems resources. Psychosocial consequences of the disease can be significant.

Nowadays, given that there is no uniform reporting standards, the medical world is facing the absence of real data on the epidemiology, natural history and treatment of chronic venous disease. The real incidence of severe manifestations of chronic venous disease, such as venous ulcers, it is difficult to assess. Overall prevalence of venous ulcers is estimated at around 0.3% of the adult population in Western countries and increases with age, women beeing more affected with a women-men ratio of 2:1 to 3:1. About 14% of patients with chronic venous disease develop venous ulcers. Although the pathophysiology of chronic venous disease is incompletely known, chronic venous hypertension is generally accepted as the predominant cause, trophic skin changes culminating with venous ulcers. Understanding disease complex pathogenic process and clinical manifestations is the key to patient assessment and management. Management of patients with chronic venous disease is difficult given that, to date, there is no clear evidence about the risk factors associated with disease progression.

Venous ulcer is the most severe and disabling complication of chronic venous disease, defined as a defect of the entire skin thickness, most frequently located in the ankle region, with no tendency to spontaneous heal, maintained by the chronic venous disease. Venous ulcer is the most frequent cause of ulceration of the lower leg in developed countries - about 75% of all leg ulcers, affecting about 1% of the general population and 3% of the elderly. Most venous ulcers are difficult to heal and about 68% have a tendency to relapse after a period of 2 years. Venous ulcers are a major health problem both in relation to prevalence and socio-economic impact and the associated morbidity. Socio-economic impact of venous ulcers is significantly, resulting in impairment of patient ability to sustain social and occupational activities, decreased quality of life and financial constraints. Venous ulcers are treated at both the outpatient and inpatient level, by dermatologists, family physicians, internists, geriatric physicians and vascular surgeons. Multiple treatment options have been proposed to address venous ulcer. Compression therapy, most popular and most used form of treatment, is identical to the one introduced by Unna in 1885. The principle of compression bandage is based on the argument that the application of an external compression - 30 - 40mmHg - increased interstitial pressure and decreases venous return of blood to the venous system. Most studies in this regard argue that the use of compression is

essential not only for patients with ulcer but for all patients with chronic venous disease. However, this is not always effective, cure rates varying greatly published between 40-95%.

Currently, there is a unanimous consensus and, moreover, a recommendation for the use of compression for patients with active and healed venous ulcers, given the existence of clear evidence supporting the fact that ulcers heal more quickly and recurrence rates are significantly reduced compared to any other therapies.

GENERAL PART

Concerns for the study of risk factors associated with failure to obtain or delayed healing ulcer, goes back more than two decadesc chronicity and surface being among the most studied and incriminated. Although the surface and chronicity are important parameters, this does not help us much in understanding why some patients do not heal. A particular reason to identify other factors which prolong the healing is that we may be able to modify them to improve results.

Although, several factors have been identified as being responsible for healing failure or prolonged healing there is a high degree of variability between data reported. Things are more complicated since there is a large variability in terms of results obtained in patients with similar disease patterns identically treated.

In terms of the prognosis of chronic venous disease C6 in terms of healing, the data available in the literature claim that about 70% of venous ulcers heal within 24 weeks under conditions of optimal therapeutic strategies. Early identification of prognostic indicators would be useful to identify potential healing ulcers and to enable the rapid implementation of appropriate therapeutic strategies.

A number of factors clinical, imaging and psychosocial features have been described in the literature:

— low level of physical activity seems to be a risk factor associated with venous ulcer healing, without clear scientific evidence. We could say that reducing the level of physical activity is associated with a calf muscle pump impairment, but can not establish a relationship of dependency. Limiting physical activity does not necessarily imply calf muscle pump impairment, reduction of ankle joint mobility being more effectively correlated;

— ankle joint mobility limitation is described as a risk factor for venous ulcer occurrence. Regarding healing, no solid conclusions can be done, due to inconsistencies and the impossibility of comparing results of studies;

— venous pathophysiology - results are mixed and dependent on the type of vein pathology; comparing the results is difficult because of significant variations in assessment of vein pathology, inclusion criteria in studies and because, over time, the criteria for defining reflux have changed. However, deep venous pathology - reflux, obstruction - is associated with the risk of non-healing;

— the status of nutrition and weight - patients with venous ulcers exhibit low levels of vitamins C and A, carotene and zinc, but this deffiecencies were not evaluated for healing

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risc. Obesity can contribute to ulceration by affecting calf muscle pump, but there is no sufficient data to support this hypothesis;

— duration of ulcers – ulcers older than 3 months are prone to healing failure;

— ulcer size - there is controversy regarding the failure of the ulcer healing, but the data suggest that the area > 20cm2 and depth > 2cm have risk of treatment failure at 24 weeks;

— reccurent ulcer – the are are conflicting data with regard to influence of ulcer reccurency on ulcer healing;

— ulcer bed and exudate - the presence and quantity of granulation tissue, necrotic tissue or exudate not significantly correlated with the risk of failure of healing at 12, 24 or 52 weeks;

— surgical/ enzimatic - seem to have a negative effect on healing;

— infection - there is evidence to suggest that infection has an impact on healing;

— surrounding skin - data from the literature are contradictory regarding the influence of edema and / or extensive lipodermatosclerosis on ulcer healing;

— compresion thetapy - increases the chances of healing, multicomponent systems being more efficient than single layer systems;

— age / ethnicity / gender - in terms of age and ethnicity data is inconclusive; gender does not appear to be a predictive or risk factor for healing;

— psychosocial factors - given the relative lack of studies a relationship of dependency between psychosocial profile and healing can not be established.

Although in the past 20 years, the management of venous ulcer has changed greatly and that there is concern about the risk factors for delayed healing, most evidence from the literature is inconclusive.

The only factors identified and unanimously recognised to delay healing are represented by ulcer size - especially ulcers larger than 20cm2 – old ulcer - more than 3, 12 and 24 months – reccurent ulcer and the presence of deep venous pathology - reflux and / or obstruction.

PERSONAL STUDY

OBJECTIVES

This paper aims to identify factors that influence venous ulcer healing, treated according to current recommendations.

Identifying risk factors for healing failure may establish the opportunity to appreciate treatment outcomes and allow patient information on the objectives, manner and treatment expectations.

MATHERIALS AND METHODS

The study material consisted of data from venous leg ulcer patients hospitalized in the Dermatology Department, Clinical Emergency County Hospital Craiova. For each individual patient, date on sociodemographics, medical history, ankle-brachial index, imaging examination, disease course and ulcers characteristics, physical activity, ankle joint mobility, specific self-care activities in relation to disease management, were colected. Reassessment intervals were set at four weeks or less, if applicable (eg., treatment adverse events, rapidly progresive disease, etc.). At each assessement data on ulcer parameters, disability, psychosocial and treatment compliance were collected.

For data processing we used Microsoft Excel (Microsoft Corp., Redmond, WA, USA) with XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 software (IBM Corporation, Armonk, NY , DOOR).

Information obtained was stored in Microsoft Excel files, and then statistically processed in order to analyze the relationships between clinical and laboratory data of patients.

Secondary processing of data - descriptive analysis of the lot based on various parameters, calculating statistical parameters, mean and standard deviation, their graphic representation - was performed with Excel, using the controls Pivot Tables, Functions, Statistical, Chart and module Data Analysis. To achieve complex statistical tests (Chi square test / Fisher exact test, Student) I used module XLSTAT or SPSS.

To characterize the numerical data used for this paper, we used statistical indicators fundamentals: arithmetic mean and standard deviation.

RESULTS

This study was prospective, included 83 consecutive patients with venous ulcers and tried to identify additional factors predictive for healing failure at 24 weeks under standard therapy.

Demographics shoved a higher incidence in men – men 62.65% vs. 37.35% female and in urban areas - 65.06% urban vs. 34.94% rural. Higher incidence in males was in contradiction with results of previous studies conducted on large samples, mentioning female gender as a risk factor for chronic venous disease advanced.

Also, a higher prevalence was noted in the age group 60-69 years - 34.94% of patients. Comparing distributions by age groups for patients with healing in less than 24 weeks and those with healing in more than 24 weeks, we found no statistically significant differences (p = 0.582).

Although there is a small numerical difference between the average age of the patients who healed in less than 24 weeks, and those with healing over 24 weeks, it is not statistically significant (p = 0.409). Therefore, we can not say that age is a factor that has a major impact on the healing process.

There was no statistically significant difference between patients according to sex, neighter Fisher test result (p = 0.651), nor OR value (OR = 1.31, 95% CI = 0.54 to 3.20 with which includes the value 1) having no statistical significance.

We could not prove a statistically significant differences between patients from rural or urban area (p = 0.359> 0.05), (OR = 0.61, 95% CI = 0.24 -1.52).

When comparing distributions of the subgroups depending on the education level - elementary, medium, high - by Chi square test, we had a result that did not indicate statistically significance (p = 0.690). In conclusion, level of training is not a parameter that provide useful clues about how will heal.

The BMI is not predictive of the risk of non-healing at week 24, mean BMI was being similar between the two groups of patients, $31,91 kg / m^2$ in patients who healed in more than 24 weeks and $31 , 28 kg / m^2$ in those who healed in less than 24 weeks.

There was no statistically significant difference between patients with or without a history of deep vein thrombosis, (p≈1, OR = 1.33, 95% CI = 0,28-6.36).

There was no statistically significant difference between patients with or without popliteal vein reflux (p = 0.827, OR = 0.87, 95% CI = 0,37-2.06).

There was no statistically significant difference between patients with or without varicose veins (p = 0.187, OR = 0.53, 95% CI = 0,22-1.27).

Patients who had vascular surgery showed higher proportion of healing lasting over 24 weeks, but the difference was not statistically significant (p≈1, OR = 1.20, 95% CI = 0.34 to 4.29).

There was no statistically significant difference between patients with or without ulcer surgical debridement (p≈1, OR = 1.33, 95% CI = 0.28 -6.36).

Patients with lipodermatosclerosis were more prone to heal above 24 weeks (p = 0.000058, OR = 7.07), over 70% of patients with lipodermatosclerosis had healed afer 24 weeks, vs 25% of patients without had healed after 24 weeks. Therefore, we can say that lipodermatosclerosis is a poor prognostic factor. The facts are similar with patients showing stasis dermatitis (OR = 11.53, with a 95% confidence interval = 1.39 to 95.79 CI).

Patients with recurrent ulcer presented in greater proportion of healing lasting more than 24 weeks, but the difference was not statistically significant (p = 0.359, OR = 1.64, 95% CI = 0.66 to 4.09).

Although patients who received compression presents greater percentage healing in less than 24 weeks, the difference was not statistically significant (p = 0.189, OR = 0.53, 95% CI = 0,22-1.27). Lack of compliance to compression therapy was associated with a higher risc of not healing at 24 weeks (p = 0.027, OR = 0.35, with 95% CI = 0.14 to 0.85). Analyzing patients healing in less than 24 weeks and those with healing in more than 24 weeks by Student t test, we identified a statistically significant difference between the two groups of patients in terms of duration of the ulcer (p = 0.025 Student <0.05). So we can conclude thar ulcer duration can influence the time to heal.

There was a significant difference in terms of the ulcer area, which is higher in those who finally had a slower healing (p = 0.048).

There was a significant difference in terms of the ulcer depth, regarding healing at 24 weeks 16.07 ± 4.63 (median ulcer depth in patient wich did not achieved healing at 24 weeks) mm versus 12.54 ± 4.19 mm (median ulcer depth in patient who achieved healing at 24 weeks), (p = 0.00047).

Regarding ABPI there eas a statistically significat difference between patints who achieved healing at 24 weeks and those who did not - 1.05 (median ABPI in those who healed in more than 24 weeks) vs. 1 (median ABPI in those who healed in les than 24 weeks) (p-value = 0.041).

CONCLUSIONS AND DISCUTIONS

Ulcer duration, surface and depth and a low ankle-brachial index showed statistical correlation with healing failure at 24 weeks, and this result is recognized by other studies.

The study results confirm the importance of ulcer duration and surface as prognostic factors for ulcer healing at 24 weeks and also the importance of compliance to standard compression therapy. These factors are modifiable, if medical education of patients with chronic venous disease would focus on the importance of patient early presentation as soon as the ulcer has installed, given the fact that there is a direct relationship between the duration of ulcer and its surface. Regarding compliance to standard compresion therapy, medical personnel involved in the management of the condition should focus on explaining to the patient the benefits on ulcer healing and on the risks associated with poor compliance.

Given the fact that the venous ulcer is specific to older ages, that altered arterial circulation is also common in elderly, that the presence of both vascular disease is not random in those patients and that the results of this study confirms that a low ankle-brachial index is

associated with healing failure at 24 weeks, a complex therapeutic management of both vascular disease, is required.

The association of venous ulcer with trophic skin lesions – stasis dermatitis and extensive lipodermatosclerosis - outlines a clinical profile associated with healing failure at 24 weeks. This type of skin lesions commonly occur in patients with advanced and neglected chronic venous disease.

We can speculate beneficial effect of early identification of patients with chronic venous disease with aggressive pattern of evolution and the establishment of a comprehensive monitoring and treatment program. To achieve such an objective there is a need for studies focused on the primary or secondary disease risk profile and on potentially modifiable factors.

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