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SYMPHYTUM OFFICINALE IN THE TREATMENT OF PLANTAR KERATOSIS IN DIABETIC PATIENTS: DOUBLE BLIND RANDOMIZED CLINICAL TRIAL

Clinical Research

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ABSTRACT

PURPOSE: To compare the efficacy between SO and salicylic acid SA in the treatment of plantar keratosis of diabetic patients. **METHODS:** Randomized, double-blind clinical trial, with 47 type 2 diabetic patients, both sexes and with plantar keratosis. Patients were randomized into 2 groups: G1 (n = 48; treated with 15% SO extract) and G2 (n = 46; treated with 10% AS). The feet were photographed before (D0) and after the treatment (D30) and keratosis areas were measured using the Image J software. For each patient, a lesion in each foot was analyzed. The results were expressed by median. In the statistical analysis, the Wilcoxin test was used to compare the lesion areas before and after treatments and the Mann-Whitney test was used to compare the regression of the lesion areas between the two groups. P <0.05 was adopted. **RESULTS:** G1 (D0 = 8.156 vs D30 = 2.226; p <0.0001) and G2 (D0 = 4.835 vs D30 = 2.059; p <0.0001) showed a difference between the areas (cm^2) of the keratosis, before and after the treatment. There was a difference in the regression of the areas (cm^2) of keratosis, between G1 and G2, respectively (4.540 vs 1.171, p <0.0001). **CONCLUSION:** Symphytum officinale proved to be more effective than Salicylic Acid in the treatment of plantar keratosis in diabetic patients.

KEYWORDS

Keratosis. Diabetes Mellitus. Medicinal Plants

INTRODUCTION

The plantar keratosis in diabetic foot is caused by a process termed hyperkeratosis which is defined as an accelerated proliferation of epidermal cells, creating a stronger cohesion of the cells, decreasing the rate of desquamation and consequently leading to a hypertrophy of the stratum corneum[1]. This process is stimulated by recurrent traumas and the persistent abnormal foot pressures that is common in diabetics patients with motor neuropathy. The trauma and abnormal pressures on the foot results from the motor neuropathy that leads to deformities on foot and from the lack of sensation originate from the sensory neuropathy. Diabetic patients with plantar keratosis have a significantly increased risk in developing foots ulcers, the relative risk for ulceration in a callused area is 11.0 when compared to normal areas. Because of the mechanical overload of the foot, the process of ulceration initiates when the connections between the callus cells become separated and lead to skin tears and blisters[2,3].

In this context, the treatment of diabetic foot complications has a high coast and in many cases the amputation is the only option. In a Brazilian study, realized at a public hospital, an average cost of USD $ 800 per patient was calculate for the hospital treatment of diabetic foot. The prevention of this condition has an importance in individual and collective levels, reducing coast with hospitalization, reducing the amputation and improving the patient's life quality[4].

The assessment of the foot of diabetic patient is recommended for prevention and in addition to the neurological, vascular and foot shape examination, a dermatological analysis is necessary, and the plantar keratosis is one of the findings that needs to be searched[5].

Preventative strategies for plantar keratosis are very important in diabetic patients with peripheral neuropathy. Identify early the osteoarticular deformities that provides higher pressure points and areas of altered sensitivity is part of the evaluation. The reduction of pressure and redistribution of weight-bearing load over an increased area of the foot can be achieved through appropriate footwear, orthotic devices and insoles[5].

The treatment of keratosis includes the use of topical keratolytic drugs or surgical debridement[6]. Among the drugs, the salicylic acid solutions have widespread use[7]. Topical salicylic acid has keratolytic properties and it is used as a keratolytic agent is its main indication in dermatology. To treat localized keratoses the concentrations of the preparations vary from 10 to 40%. However, this medication can cause hypersensitivity reaction and percutaneous absorption, with the possibility of systemic action [8,9].

In 2006, the publication of The National Policy for Medicinal and Phytotherapeutic Plants (NPMPHM) established guidelines and priority lines for the development of technologies and innovations in this field and actions for the rational use of medicinal plants and herbal medicines strengthening production chains[10]. Attention to alternative treatment possibilities would lead to an improvement in health care population, providing another forms of treatment and prevention[11].

Symphytum officinale, popularly called comfrey, belongs to the *Boraginaceae* family, being a perennial plant that was introduced in Brazil, where it adapted. It can be found in Asia, Europe and North America[12,13]. The plant contains therapeutic properties as anti-inflammatory, healing, moisturizing, antiseptic, bactericidal, fungicidal, antipruritic, soothing and antioxidant. Most of its therapeutic properties are attributed to the substance allantoin which stimulates cell proliferation, tissue regeneration, has an anti-inflammatory, healing, emollient, moisturizer and keratolytic effect[12,14,15]. The *S. officinale* extract is non-toxic, reduce the excess of reactive oxygen species and its use in human skin is safe and have beneficial effects[13].

Studies have revealed that 0.5% of 6 Symphytum officinale leaves used in a rat diet are sufficient to induce spleen and liver cancer. Mattocks [16] detected the presence of pyrrolizidine alkaloids with toxic properties in *Symphytum officinale* and found that symphidine alone behaved as cancer-inducing in rats. According to this author, the leaves and the roots proved to be carcinogenic. Due to the toxicity of *Symphytum officinale*, which occurs due to the presence of these alkaloids pyrrolizidines, several studies recommend only the topical use and have demonstrated that permeation dermis of toxic substances does not occur[17-22].Considering systemic toxicity, the Agency National Health Surveillance Agency limited the use only to topical preparations[23].

The aim of this study was to compare the use of *Symphytum officinale* and salicylic acid in the treatment of plantar keratosis in diabetic patients.

METHODS

The study was designed as a prospective, double-blind, randomized controlled clinical trial performed at the Municipal Center for Education in Diabetes, in the city of Pouso Alegre, Minas Gerais, Brazil, in the period of March 2017 to July 2020. The research was approved by the Ethics and Research Committee of the University of Vale do Sapucaí (CAAE: 65431417.4.0000.5102) and followed the precepts established by Resolution No. 466/12 of December 12, 2012 of the Ministry of Health.

The inclusion criteria were plantar keratosis in a patient with type 2 diabetes mellitus (Dm2). Patients with ulcerated lesions and /or amputation in the feet, patients with type 1 diabetes mellitus, gestational or other types of diabetes were not admitted. Other exclusion criteria were those who refused to give informed consent or had any skin conditions on their feet during the use of the product. All patients provided informed consent after the aims of the study had been explained to them.

The sample consisted of 47 patients that were randomly allocated in two groups: group 1 (G1) composed of 24 patients, treated with the extract of Symphytum officinale and group 2 (G2) composed of 23 patients, treated with salicylic acid.

The random allocation list was kept confidential by the pharmacist responsible for handling the products and placed in opaque and sealed envelopes, which were numbered so that all could be counted at the end of the study.

The Symphytum officinale extract was prepared at the Botany laboratory of University of Vale do Sapucaí. The leaves of the plant were dehydrated at 45 ˚C, in an appropriate oven. Then it was added to the dehydrated leaves 400 ml of ethanol and 100 ml of distilled water (for each 20 grams of leaves). This mixture was processed through the Soxhlet apparatus, which produced the extract. The extract was taken to the appropriate oven, at a temperature of 45 ˚C, where it remained for 48 hours.

At the compounding pharmacy, the products were prepared to be used in G1 and G2 with the following proportions: extract of Symphytum officinale 15%, petroleum jelly 40 grams and five drops of green dye; salicylic acid 10%, petroleum jelly 40 grams and 5 drops of green dye.

Patients had their feet examined and subsequently received guidance about the use of the product and collection at the compounding pharmacy. These patients were instructed to apply a thin layer over the entire plantar extension, including the lateral areas of the heel and fingers (except the interdigital region), once a day (at night), for 30 consecutive days. They received an opaque, sealed and numbered envelope to be delivered at the pharmacy to the pharmacist responsible for product withdrawal.

The feet of the participants, from both groups, were photographed before (D0) and after treatment (D30) and the keratosis areas were measured in the photos, using the Image J software.

The results were tabulated and stored in the Excel for Windows software and the variables were submitted to statistical analysis using the Bioestat 5.4 software. The data obtained were expressed as median. For the comparison of related variables, the Wilcoxon test was used and for the comparison of independent variables, the Mann-Whitney test. Finally, the D'Agostino Pearson Test was used for normalities of the variables, adopting a value of $p < 0.05$, with rejection of the null hypothesis.

RESULTS AND DISCUSSION

Three patients were excluded from the research because they did not return after 30 days of treatment. With a sample of 47 patients with DM2 and plantar keratosis, it was found that most patients were female (58%), aged 60 years or over and less than 70 years (58%), and more than 10 years of diabetes (90%).

Comparing the areas with plantar keratosis, from the median given in square centimeters (cm²), of diabetic patients, before (D0) and after (D30) the treatment with *Symphytum officinale* cream (G1) and salicylic acid (G2) , the following results were obtained: for G1 (n = 24) in the D0 = 8.156 cm² and in the D30 = 2.226 cm² and for G2 (n = 23) in the D0 = 4.835 cm² and in the D30 = 2.059 cm², both groups with p = 0, 0001 (Table 01).

The comparison between the regression of areas with plantar keratosis, based on the median given in square centimeters (cm²) and percentage, of diabetic patients, after treatment (D30) with *Symphytum officinale* cream (G1) and salicylic acid (G2), presented the following results: for G1 (n = 24) the median regression of lesions was 4.540 cm² and for G2 (n = 23) 1.171 cm² with p = 0.0001; and the median percentage of regression was 65.240% in G1 and 44.580% in G2 with p = 0.0076 (Table 02).

According to the results obtained, it was found that the areas with plantar keratosis of patients with DM2 who used the cream based on *Symphytum officinale* regressed more, both in absolute value (cm²) and in percentage, than the area of those who used salicylic acid-based cream. The results were found to be significant (p <or equal to 0.05).

Therapeutic properties of *Symphytum officinale* have already been established, its use as an emollient and keratolytic deserves attention. The presence of the active allantoin in its composition is an indicator that its properties can be effective in the treatment and prevention of plantar keratosis of diabetic patients[12].

Considering the importance of treating keratosis plantar of diabetic patients as preventive measure of the appearance of ulcers and consequent amputations that represent a high cost for the public health system, in addition to interfere negatively in the quality of life of patients and knowing the importance of using medicinal plants and herbal medicines for the treatment and prevention of conditions, in view of public health policies health, the development of this study is justified[14].

Table 01 – Comparison between areas with plantar keratosis (median) of diabetic patients, before (D0) and after (D30) the treatment with *Symphytum officinale* cream (G1) and Salicylic Acid (G2).

Variables	D0	D30	*p*
Area with plantar keratosis (median in cm²) – G1 (n=24)	8,156	2,226	0,0001
Area with plantar keratosis (median in cm²) – G2 (n=23)	4,835	2,059	0,0001

Table 02 – Comparison between regression of areas with plantar keratosis, of diabetic patients, after treatment (D30) with cream based on *Symphytum officinale* (G1) and Salicylic Acid (G2).

Variables	G1 (n=24)	G2 (n=23)	*p*
Plantar ketatosis regression (median in cm²)	4,540	1,171	0,0001
Percentage of regression (%)	65,240	44,580	0,0076

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