

The Role of Pentoxifylline on Distal lower Extremities Ulcers

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Abstract: Venous ulcers are the major occurrence of chronic wounds, occurring in 70% to 90% of leg ulcer cases. Venous ulcers develop mostly along the medial distal leg, and can be very painful with significant effects on quality of life. Venous ulcers affect approximately 1% of the world's population, increasing health care expenditures and decreasing quality of life. Several hypotheses may help explain their origin. Insufficient veins or valves or impaired muscle function may lead to abnormal calf muscle pump function that can elevate ambulatory venous pressure.

The aim of this study is to evaluate the efficacy of pentoxifylline in treating chronic venous ulcers specially of lower extremities.

Keywords: Compression Therapy, Pentoxifylline, Ulcers.

Methods: From Nov 2013 to October 2015, 80 patients with chronic venous ulcers were randomly assigned to 2 groups: a standard treatment group that received compression therapy or an intervention group that received oral pentoxifylline (400 mg, 3 times daily) in addition to compression therapy. Time duration of wound healing, edema, pain, and ulcer size in the 2 groups were studied.

Results: The median duration of complete wound healing was 4 months in the intervention group and 6.25 months in the standard treatment group. Recovery from pain and edema was not statistically significant after 3 months' follow-up in either group. After 3 months of treatment, ulcer size decreased more in the intervention group compared to the standard treatment group. Pentoxifylline in association with compression therapy decreases both time to complete wound healing and ulcer size.

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I. Introduction

Ulcers of the lower extremities, particularly in individuals older than 65 years, are a common cause for visits to the podiatrist, wound care specialist, primary care physician, vascular surgeon, or dermatologist.

Venous ulcers affect approximately 1% of the world's population, increasing health care expenditures and decreasing quality of life(1). Several hypotheses may help explain their origin(2,3). Insufficient veins or valves (dysfunctional valves in the veins that allow backward blood recirculation due to incomplete valve closure) or impaired muscle function may lead to abnormal calf muscle pump function that can elevate ambulatory venous pressure (venous hypertension(4)). This hypertension subsequently results in local venous dilatation and pooling, concomitantly trapping leukocytes that may release proteolytic enzymes that destroy tissue. Venous pooling also induces interendothelial pore widening and deposition of fibrin and other macromolecules that trap growth factors within them, rendering them unavailable for wound repair. Compression therapy, the mainstay treatment, reduces edema, reverses venous hypertension, and improves calf muscle pump function. Several treatment options can be employed as adjuvants to compression, such as systemic therapy with pentoxifylline or aspirin, autologous grafts, tissue-engineered skin, growth factor therapy, and/or vein surgery(5).

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease(6,7,8). Although it is often classified as a vasodilator, pentoxifylline's primary action reduces blood viscosity, probably due to its effect on erythrocyte deformability, platelet adhesion, and aggregation(8-11). Pentoxifylline also inhibits production of cytokine tumor necrosis factor alpha (TNF-a), a property currently under investigation in a number of diseases. The most common adverse effects are nausea, gastrointestinal disturbances, dizziness, and headache. Studies suggest that pentoxifylline may be effective in increasing the healing rate of chronic venous ulcers with or without compression therapy but at a higher dose than is used for treating claudication (400 mg, 3 times daily)(12). In the present study, we evaluated the effect of pentoxifylline on the time to complete healing of chronic venous ulcer.

II. Material and Methods

From November 2013 to October 2015, 80 patients were diagnosed with chronic venous leg ulcers in Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India. Forty patients were randomly allocated to compression therapy (standard group) and forty to pentoxifylline with compression therapy (intervention group). Randomization was performed by means of sealed opaque envelopes containing computer-generated random numbers. The standard treatment group received only compression therapy and the intervention group received oral pentoxifylline (400 mg, 3 times daily) in addition to compression therapy. Mean age of patients was 37.5 ± 8.5 years in the intervention group and 36.9 ± 11 years in the standard treatment group. The exclusion criterion was arterial insufficiency that was ruled out by Doppler ultrasound imaging.

Pain was assessed by a numerical rating scale in which the patient was instructed to choose a number from 0 (no pain) to 20 (unbearable pain) that best described their current pain(14).

To assess leg edema(14) the examiner pressed his fingertip against a bony prominence for 5 seconds, and then removed it. A residual indentation indicated pitting edema, which was graded on a scale of 1 (mild) to 4 (severe). Questionnaires were used to collect data. Patient's pain, edema, and ulcer size were recorded at their first clinic visit, as well as 1 and 3 months after treatment. Patients were instructed to refer to the hospital monthly, and time duration of complete wound healing was recorded.

III. Results

Mean time to complete wound healing in the intervention and standard treatment groups was 4 and 6 months, respectively, and was statistically significant. Edema at the first clinic visit was higher in the intervention group but was not statistically significant. At 3 months' follow-up, edema had subsided in 75% of patients in the intervention group and in 50% of patients in the standard treatment group. Although the differences never reached statistical significance, recovery from edema was better in the pentoxifylline (intervention) group. Mean degree of pain at first clinic visit, 1 month, and 3 months after treatment was 14, 11, and 9, respectively, in the intervention group and 12, 9, and 8, respectively, in the standard group. Although mean degree of pain decreased more in the intervention group, it was not statistically significant. Additionally, the mean ulcer size at the first clinic visit, 1 month, and 3 months after treatment was 8.69, 5.30, and 1.41, respectively, in the intervention group and 8.66, 6.15, and 3.78, respectively, in the standard treatment group, which was statistically significant.

IV. Discussion

Treating venous ulcers represents a therapeutic challenge, the immediate goal of which is to restore epithelium. Compression dressings (bandages) are the mainstay treatment for chronic venous ulcers. The goal of compression is to increase venous ulcer healing by improving venous return and reducing edema of the lower extremities. Several systemic adjunctive treatments may be used in conjunction with compression therapy. Pentoxifylline has been shown to decrease white blood cell adhesion and activity, blood viscosity, platelet aggregation, and pro-coagulation and to increase fibrinolytic activity. Pentoxifylline is metabolized in liver and red blood cells to 7 active metabolites. Studies suggest it may be effective in treating venous ulcers. When pentoxifylline plus compression was compared to placebo plus compression therapy healing rates were 64% and 34%, respectively(15).

The results of the present study show that pentoxifylline plus compression therapy decreases the time to complete wound healing. In a 6-month randomized placebo-controlled trial comparing pentoxifylline (400 mg, 3 times daily) with compression to placebo with compression in 172 patients, Belcaro et al(12) found that patients treated with pentoxifylline showed significantly greater healing (67% versus 30.7%). Treatment with pentoxifylline also was determined to be more cost effective. Falanga et al(16) reported the effect of compression bandaging plus pentoxifylline 800 mg, pentoxifylline 400 mg, and placebo 3 times a day for 6 months. Pentoxifylline was well tolerated at both doses, but patients healed faster with the 800 mg dose. In a 12-month randomized, placebo-controlled trial comparing pentoxifylline (400 mg, 3 times daily) with compression versus placebo with compression in 85 patients, Desanctis et al(17) found significantly higher healing in the pentoxifylline group (88% versus 44%). No significant side effects from using pentoxifylline were reported. Jull et al(18) published their results of a systemic review of all randomized, controlled trials using pentoxifylline for venous ulcers. Pentoxifylline was shown to be beneficial when used in conjunction with compression therapy and may be efficacious as monotherapy.

In the present study, edema and pain at the first clinic visit was more severe in the intervention group and decreased more after 3 months' follow-up compared to the standard treatment group, but the differences were not statistically significant. The effects of pentoxifylline on lower extremity edema in patients with chronic venous ulcers were not evaluated in the previous studies.

V. Conclusion

The results of the present study have shown pentoxifylline in association with compression therapy is beneficial in increasing the healing rate of chronic venous ulcers specially in lower extremities. As previously mentioned, systemic abnormalities in fibrinolysis, seen in patients with venous disease, contribute to the "pericapillary fibrin cuff," which also may act as an additional perfusion barrier to oxygen and nutrients. Perhaps the fibrinolytic effect of pentoxifylline affects the pericapillary fibrin cuff, and subsequently increases the healing rate of chronic venous ulcers.

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