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PENTOXIFYLLINE'S IMPACT ON VENOUS ULCERS: A RANDOMIZED STUDY.

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Abstract.

Objective:

To study the effect of pentoxifylline versus placebo on venous leg ulcers with and without compression therapy.

Methods :

Prospective study of factorial design, permitting the simultaneous evaluation of alternative pharmaceutical, bandaging, and dressings materials. The study took place at the Department of General Surgery, I.G.I.M.S., Patna. A total of 40 patients with confirmed venous ulcers were included, after excluding other major causal factors. Participants were randomly assigned to receive either pentoxifylline or a placebo. The main outcome measure was the complete healing (full epithelialization) of all ulcers on the study leg.

Results:

Among the patients receiving placebo, 10 out of 19 (53%) achieved complete healing, while among those receiving pentoxifylline, 14 out of 21 (64%) achieved complete healing.

Conclusions:

The study found no significant difference in healing rates between patients taking pentoxifylline and those receiving placebo.

Recommendation:

It is compression therapy that heals the ulcer, not the dressing, so wherever possible the primary dressing of choice should be a simple knitted viscose one. This recommendation may not apply if the wound has high levels of exudate or slough.

Keywords: Venous ulcer, pentoxifylline, wound healing, compression therapy, ulcer size, Submitted: 2023-09-14 Accepted: 2023-09-20

1. INTRODUCTION.

Venous ulcer is a serious clinical expression of habitual venous insufficiency. It is accountable for 70% of habitual ulcers that do not heal within 6 weeks. There are numerous sources of chronic ulcers including rheumatoid arthritis, trauma, arterial insufficiency, sickle cell disease, diabetes mellitus, chronic osteomyelitis, vasculitis, and skin tumor [1]. Venous ulcer is a very common cause of lower extremity ulceration, which affects approximately 1% population in most countries, and the incidence rate increases with age and female gender [2].

According to the few Indian studies that were carried out on the epidemiology of chronic wounds, a study claimed the prevalence at

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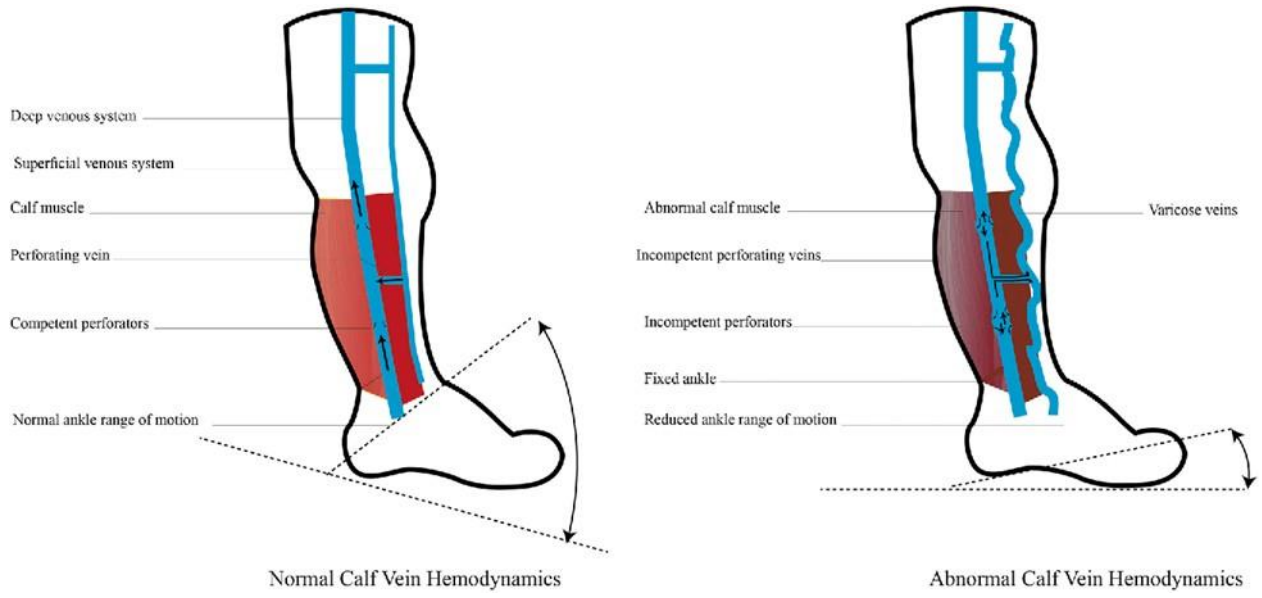

Figure 1: **Venous disease Calf vein hemodynamics.**

4.5/1000 population, while the prevalence of acute wounds was 10.5/1000 double the popula- tion. The main cause of Indian ulcers was found to be due to venous etiology which is followed by other factors like filariasis, tuberculosis, and leprosy [3].

The principal threats for venous ulcer development are older age, obesity, previous leg injuries, deep venous thrombosis, and phlebitis [4]. About 80% of all chronic leg ulcers are venous leg ulcers which causes a reduction in health-related quality of life [5]. Different types of treatment for venous ulceration have been developed over the years including local ulcer treatment, compress, ion, and drug therapy. Development in tissue engineering has evolved and now new living tissues can be developed for cutaneous wound repair and skin replacement.

Data obtained from a small pilot study suggested that Derma graft and compression therapy is more beneficial in healing venous ulcerations than compression therapy alone [6]. Many orthodox home remedies are used in India like honey, neem oil, boiled potato peel, and many more. There is no evidence-based study of their usefulness. Potato peel dressing protects from the external environment thereby keeping the wound from any further infections. The honey-impregnated dressing is used for its antibacterial/antiseptic properties [7].

Drugs that have been found beneficial for venous disease are pentoxifylline and aspirin when used in conjugation with compression therapy. Pentoxifylline has strong hemorrheologic properties and is a methylxanthine derivative [8]. Pentoxifylline can be used three times daily combined with compression therapy. It acts by reducing in viscosity of blood leucocyte metabolism, inhibiting platelet aggregation, and consequent improvement in microcirculation [9].

The increasing load of venous ulcer patients on our health system and various research being conducted, this study will be conducted to observe the effect of pentoxifylline on venous ulcers in our department of general surgery, I.G.I.M.S.

1.1. Aims and objective.

To study the effect of pentoxifylline versus placebo on venous leg ulcers with and without compression therapy. Study the incidence of VLUs (sex and age distribution) in the Department of General Surgery, I.G.I.M.S., Patna.

2. MATERIAL AND METHODS.

A prospective study will be conducted on 40 patients in the Department of General Surgery,

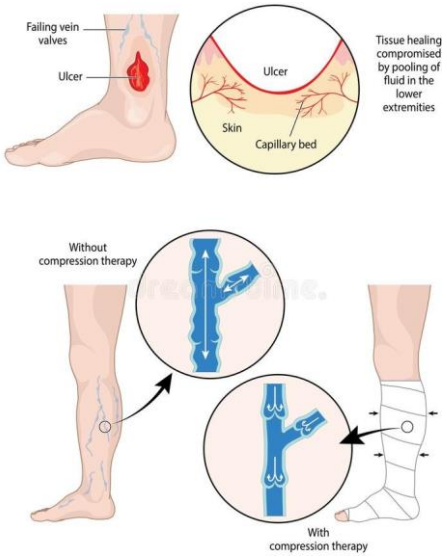

Figure 2: **MOA of Compression therapy.**

I.G.I.M.S., Patna comparing pentoxifylline with the placebo with or without compression bandaging on the patients suffering from venous leg ulcer and dividing the total number of patients into 2 groups A and B. Patients will be random- ized to receive either pentoxifylline or placebo and they will also be randomized to either receive or not compression bandaging. The study will be conducted between July 2020 to December 2020. Each patient was given a patient number.

The effect of the drug on treating the patient will be explained and informed consent will be taken before starting the study on the patient. The duration of the study will be until, up to the complete healing of the ulcer, or up to 24 weeks of treatment. If the treatment was interrupted for 14 days during the study period, the patient would be considered withdrawn from the study and analyzed as a failure of treatment.

2.1. Data collection and variable definition.

Pain will be measured on a numerical rating scale in which "0" means no pain to "20" means unbearable pain. Patients will be instructed to choose between 0 to 20 depending upon the intensity of pain. The patient will be followed up every week to check the healing, lipodermatosclerosis, eczema, edema, pigmentation, and atrophy blanche. Students' t-test, chi-square, or Fisher's exact test were used, where appropriate, for comparing clinical data between the 2 groups. $P \leq 0.05$ was considered significant for all tests.

2.2. Inclusion criteria.

The study was approved by the ethical committee at the center. Informed consent was obtained from each patient before entry to the study. Eligible patients were aged between 25-50 years of age with pure venous ulcers of size less than 5 cm. Pure venous ulcers were defined as those who had a venous disease that was confirmed by ultrasonography. In cases where the ulcers were bilateral, the ulcers with the largest size were considered for the study.

2.3. Exclusion criteria.

Eligible patients were aged less than 50 years. Patients having diabetes and hypertension were excluded from the study. Also, patients with the following conditions were excluded: 1) Patients with moribund obesity and 2) Patients who had undergone surgery for Varicose veins. 3) Patient who refuses to take part in the study.

2.4. Participants.

The patients with venous ulcers were included in the study depending upon the inclusion and exclusion criteria.

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Table 1: **Characteristics of pentoxifylline and placebo groups after randomization.**

Patients' characteristics	**Pentoxifylline (n=21)**	**Placebo (n=19)**
Median age	25-50	25-50
Male	7	9
Female	14	10
Years since the first ulcer	4 (1-13)	6 (1-19)
Maximum diameter of reference ulcer (mm)	26 (16-40)	28 (17-39)

2.5. Measurements of outcome.

The principal efficacy variable was the complete healing of all ulcers on the reference leg by 24 weeks of treatment. A secondary efficacy variable was time to healing.

3. RESULTS.

Overall, 21 patients were randomized to receive pentoxifylline and 19 to receive a placebo. The groups were comparable after randomization (Table 1). The age of the patient ranges from 25-50 years. There were more female participants than males in both groups. The maximum diameter of the ulcer was 26 mm and 28 mm in both groups respectively. Complete healing was observed in 10 of the 19 (53%) patients receiving placebo and 14 of the 21 (64%) patients receiving pentoxifylline. No symbolic differences were found in the groups. The mean duration of complete wound healing is presented in Table 2.

13% of ulcers healed during the first 6 weeks period and there was no difference between placebo and pentoxifylline groups. The difference in healing rate between the two groups became significant after further weeks with more healing found in the pentoxifylline group (Figure 3).

Half of the patients were ulcer-free by week 15 for placebo and week 11 for pentoxifylline. The change in mean ulcer size is represented in Table 3.

There was no interaction between the bandage and the drug. There was a similar dropout rate in both treatment groups. 28 % was the overall side effect rate for both treatment groups. Only gastrointestinal side effects were observed more in the pentoxifylline group. The drug was acceptable to most patients and safe. The result of this study shows that pentoxifylline with compression therapy decreases the time for complete ulcer healing.

4. DISCUSSION.

The result of a field study carried out by Pemler et al on 513 patients with chronic ulcers treated with pentoxifylline, showed improvement in the reduction of symptoms like ulcer extension, coldness of the leg, paresthesia, and resting pain [10]. Pentoxifylline is absorbed in the gastrointestinal tract, completely metabolized in the body, and excreted in the urine [11].

Pentoxifylline is a methylxanthine derivative. In the United States, it is used in the treatment of intermittent claudication. Many animal and human studies are carried out using pentoxifylline showing many changes at the cellular level [8].

By inhibiting PDE and increasing the cAMP, Pentoxifylline causes vasodilation in the skeletal muscle vascular bed. Pentoxifylline is recommended with meals to minimize GI irritants [12].

In a systematic review carried out by Varatharajan et al (2016) pentoxifylline given three times a day, has promising evidence to support its use in venous ulcers [13]. As stated by Chodynicka et al (1999), pentoxiphylline is a potent, supportive, and safe drug in the treatment of leg ulcers [14]. According to Angelides (1994) pentoxifylline can be used at a dose of 1200 mg daily at the time of ulcer healing period and a low long-term maintenance dose of 400 mg daily during the ulcer-free intervals [15]. Angelides (1989) stated that pentoxifylline when given orally for 6 weeks can help in improving the persistent venous ulcer [16].

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Table 2: **Mean duration of complete wound healing.**

Group	N	Mean (months)
Pentoxifylline	21	3.25
Placebo	19	5.00

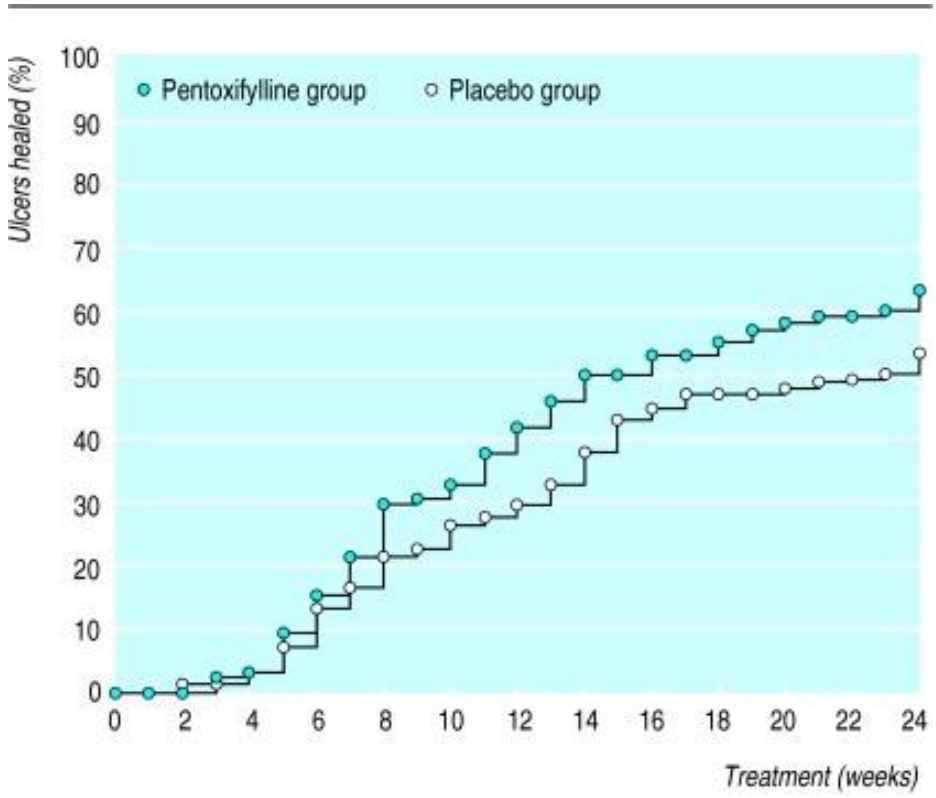

Figure 3: **Analysis of time to complete healing of all ulcers on reference leg.**

Table 3: **Change in mean ulcer size.**

Group	n	Time	Mean (cm^2)
Pentoxifylline	21	Visit 1	3.8
		3 months later	1.41
Placebo	19	Visit 1	4.2
		3 months later	3.68

Pentoxifylline is found to be a more effective alternative used for the treatment of vascular disease [17]. When compression therapy is given in conjugation with pentoxifylline, it reduces the time to heal the wound and also the ulcer size [18]. Results of the systematic review suggest that pentoxifylline can be efficacious for patients not receiving compression and give an added advantage to compression therapy for venous ulcers [19].

Data by Kamphuis et al (1994) suggest that pentoxifylline induces vasodilation in humans [20]. It was ensured that patients with only pure venous ulcers were included. Patients having serious diseases like hypertension or diabetes were excluded. A 13% ulcer healing rate was observed during the first 6 weeks. Later more healing was observed in the pentoxifylline group than in the placebo group.

5. CONCLUSION.

The study concluded that pentoxifylline has a higher rate of healing venous ulcers than placebo and healing occurred earlier in the pentoxifylline group than in the placebo group. Pentoxifylline in conjugation with compression therapy decreases the time to heal ulcer wounds. Pentoxifylline is an effective adjunct to compression bandaging for treating venous ulcers and may be effective in the absence of compression. The majority of adverse effects were gastrointestinal disturbances.

6. RECOMMENDATION.

Compression therapy heals the ulcer, not the dressing, so wherever possible, the primary dressing of choice should be a simple knitted viscose one. This recommendation may not apply if the wound has high levels of exudate or slough.

7. ACKNOWLEDGEMENT.

We are thankful to the patients; the study could not have been done without them. We are thankful to the supporting staff of our hospital who were involved in the patient care of the study group.

8. LIST OF ABBREVIATIONS.

VLU- Venous leg ulcer
PDE- Phosphodiesterase
cAMP- Cyclic adenosine monophosphate
GI- Gastrointestinal

9. Source of Funding

The study was not funded.

10. Conflict of interest.

The authors report no conflicts of interest in this work.

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