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Original Article

Efficacy and safety of oral pentoxifylline and aspirin in chronic venous and arterial leg ulcers: A 12-week randomized controlled trial

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Abstract

Background Chronic Venous and arterial leg ulcers are long-lasting wounds that significantly impair quality of life due to slow healing and recurrent nature. Several studies reported therapeutic role of aspirin and pentoxifylline individually, direct comparison of their efficacy remains limited.

Objective To evaluate and compare the wound-healing efficacy, safety, and tolerability of oral aspirin and pentoxifylline in the management of patients with chronic leg ulcers.

Methods The 12-week two-arm parallel randomized controlled trial included 62 patients with chronic venous, arterial, or mixed leg ulcers of ≥6 weeks' duration, of whom 60 completed the study. Patients were randomly allocated into two groups, one group received oral aspirin 300 mg twice daily, while the other received oral pentoxifylline 400 mg twice daily. All participants received standardized wound care. Data were statistically analyzed using Mann-Whitney U test for continuous variables and chi-square tests for categorical variables. A p-value of <0.05 was considered statistically significant.

Results Both groups exhibited a significant decrease in ulcer size over time. However, participants receiving oral pentoxifylline showed a substantial reduction compared to those receiving aspirin at 1 month (p=0.001), 2 months, and 3 months (p=0.001). Baseline pain scores were comparable between groups (p=0.789), but the pentoxifylline group demonstrated greater reduction at 2 months (p=0.007). Both groups displayed minimal pain scores after three months (p=0.293). Adverse events were also infrequent and did not show significant variation between treatment groups (p>0.05).

Conclusion Pentoxifylline proved to be more effective than aspirin in accelerating ulcer healing and reducing pain in patients with chronic leg ulcers and maintaining a favorable safety profile. The observed outcomes validate its application as a treatment alternative, particularly in cases where compression therapy is unsuitable or poorly tolerated.

Keywords Leg ulcers; Aspirin; Pentoxifylline; Ulcer size.

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Introduction

Chronic leg ulcers are a significant cause of clinical and socioeconomic burden worldwide with those secondary to venous and arterial insufficiency being a major contributor to morbidity and reduced quality of life.[1-3] Among them, venous leg ulcers (VLU) are the most common type, representing around 60-80% of all types of leg ulcers and are primarily due to chronic venous insufficiency.[4,5] Arterial (Ischemic) ulcers due to inadequate arterial blood supply are also of clinical importance but are less prevalent. In contrast, mixed ulcers including both venous and arterial ulcers are also frequently observed.[6] These ulcers frequently result from persistent venous hypertension or arterial insufficiency, leading to

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inflammation, tissue hypoxia, and eventual skin breakdown.[7] Likewise, significant peripheral artery disease (critical limb ischemia) usually precedes the onset of arterial ulcers, when tissue ischemia and ulceration occurs due to poor blood and oxygen supply. Concisely, both scenarios lead to persistent tissue hypoxia and inflammation, which hinder normal wound repair. Patients suffering from these ulcers often experience delayed healing, frequent relapses, persistent pain, and have a higher chance of infection.[8]

Epidemiologically, the prevalence of venous leg ulcers in older adults is estimated at approximately 1-3% in developed countries, and is anticipated to increase in line with population ageing and an increasing number of lifestyle-related illnesses including diabetes, obesity etc.[9,10] Sedentary lifestyle and increasing life expectancy have previously contributed to predictions that the prevalence of VLUs will rise substantially in the upcoming decades in countries such as the United States.[11]

The standard treatment for venous leg ulcers is compression therapy in which patients may experience delayed or insufficient healing. However, a number of additional pharmaceutical substances, such as aspirin and pentoxifylline, are under investigation more and more for enhanced healing results, particularly in patients with poor adherence or incomplete resolution.[3,12] Longer healing duration is also attributed to chronic venous hypertension and poor compression acceptance.[1]

Clinical studies and systematic reviews have demonstrated that pentoxifylline, a hemorheologic agents that improves blood flow, can speed the healing of venous leg ulcers, either alone or with compression treatment.[1,13] In parallel, low-dose aspirin has also been studied in pilot randomized clinical trials as an addition to conventional treatments for venous leg ulcers with the aim of improving healing time and recurrence through its antiplatelet and anti-inflammatory properties.[14,15] There is no statistically significant difference in healing time between aspirin and placebo, according to large randomized studies.[15,16] According to systematic studies pentoxifylline, either as monotherapy or in conjunction with compression intervention, also substantially speeds up ulcer healing rates.[13,17]

Furthermore, there are few direct comparative studies between aspirin and pentoxifylline for treating persistent leg ulcers, particularly in patients with arterial or mixed etiology ulcers.[13,18]

Well-designed clinical trials are needed to evaluate efficacy and safety and guide evidence-based treatment.[1] Therefore, the current study was designed to compare the safety and efficacy of oral aspirin (300 mg twice daily) and pentoxifylline (400 mg twice daily) over the period of a 12-week in patients suffering from chronic leg ulcers due to venous, arterial, or mixed insufficiency.

Methods

Study design and setting The research was carried out for a period of 12 weeks in an outpatient department of Lahore General Hospital. A total of 62 participants were recruited using non-probability consecutive sampling. Eligible consenting patients were then randomly allocated (1:1) into two groups (n=31 per group) using a simple lottery/ sealed envelope method.

Study Design Two-arm parallel randomized controlled trial and the significance level was considered to be 0.05

The final study included 60 participants, 30 from each group, who completed the study. Two participants were lost to follow-up during study as they declined to continue participation and absent from routine visits. A loss to follow-up of ≤5% was acceptable in randomized controlled trials as per cording to CONSORT guidelines and is unlikely to introduce significant attrition bias. The planned study power was maintained because the observed dropout rate (3.2%) was less than the 10% predicted during sample size calculation.

Participants were eligible for inclusion if they were 18 years or older with chronic leg ulcers persisting

for more than six weeks' duration, and demonstrated clear clinical evidence of venous or arterial insufficiency confirmed by Doppler ultrasonography. Patients were excluded if they had leg ulcers due to other etiologies such as trauma, infection, malignancy, autoimmune disease and under 18 years older, or had ulcers of less than six weeks' duration. Additional exclusion criteria included known hypersensitivity to aspirin or pentoxifylline, active bleeding disorders, pregnancy, or concurrent participation in another clinical trial.

Participants were randomly categorized into two groups: Group A received oral aspirin 300 mg twice daily, and Group B received oral pentoxifylline 400 mg twice daily. Both treatments continued for 12 weeks. Standardized wound care was applied in all patients throughout the study. The wound cleaning with saline, dressing change, and advice on limb elevation and compression stockings (if applicable for venous ulcers) was all included in care.

The primary outcome was ulcer healing, defined as a ≥50% decrease in ulcer size assessed from baseline at weeks 4, 8, and 12 using a calibrated planimeter. Ulcer edges were traced on a sterile transparent sheet to calculate the surface area in square centimeters. Photos were taken at every visit, and the same trained investigator performed all measurements to ensure consistency. Secondary results included pain relief, safety profile, and patient-reported satisfaction. Pain severity was measured using a standardized 10-point Visual Analog Scale at each follow-up visit. Safety was defined operationally as the frequency, kind, and severity of treatment-related adverse events that occurred across the research period. At every follow-up session, adverse events were noted and classified as neurological, gastrointestinal, bleeding-related, or other systemic symptoms. Adverse event (any unfavorable or unintended clinical sign, symptom, or disease temporally associated with the use of study medications) related treatment withdrawal was also recorded and regarded as a sign of poor tolerability. Patient-reported satisfaction was evaluated at the end of the 12-week treatment.

Data were entered and analyzed using SPSS version 27. Continuous variables were presented as means±standard deviation, and categorical variables as frequencies and percentages. The data normality was determined by Shapiro-wilk and the data was observed to be non-normally distributed. So, the Comparative analysis between the two groups was conducted using Mann- Whitney U test for continuous variables and chi-square tests for categorical variables. A *p*-value of <0.05 was considered statistically significant.

The study protocol was approved and reviewed by the Institutional Review Board/ Ethical Review Committee of Postgraduate Medical Institute (PGMI), Ameer-ud-Din Medical College/ General Hospital, Lahore (Approval No. 2025/EPC/48; dated 19.01.2025). Written informed consent was obtained from all participants prior to enrolment.

Results

The World Health Organization's (WHO) body mass index (BMI) classification, demographics, and prevalent clinical risk factors of participants using oral pentoxifylline and aspirin are presented in **Table 1**. There were 30 participants in each group, with over half of the members in both groups classified as normal weight based on the WHO BMI classification, with 17 individuals (56.7%) in the oral aspirin group and the same percentage in the oral pentoxifylline group. In each group, the remaining individuals (13) 43.3% were identified as overweight. The pentoxifylline group showed a slightly higher mean BMI (24.46±3.46 kg/m²) compared with the aspirin group (23.81±3.18 kg/m²). Similarly, gender classification was also comparable between groups, with males making up 53.3% (16) and females 46.7% (14). A Chi-Square test for gender distribution yielded a p- value (p>0.05) indicating that there is no significant difference in the gender distribution between the two treatment groups, suggesting that gender is equally distributed across both groups.

In the present investigation, 53.3% of the participants in the aspirin group and 46.7% of the

Table 1 WHO body mass index (BMI) classification, demographic attributes, and clinical risk factor of participants receiving oral aspirin and pentoxifylline.

Variable	*Category / Status*	*Oral Aspirin (n = 30)*	*Oral Pentoxifylline (n = 30)*	*p-values*
BMI category (WHO)	Normal weight	17 (56.7%)	17 (56.7%)	0.496
	Overweight	13 (43.3%)	13 (43.3%)	
BMI (kg/m²)	Mean ± SD	23.81 ± 3.18	24.46 ± 3.46	
Gender	Male	16 (53.3%)	16 (53.3%)	1.00
	Female	14 (46.7%)	14 (46.7%)	
Age category (years)	< 40	6 (20.0%)	5 (16.7%)	0.347
	40–59	16 (53.3%)	14 (46.7%)	
	≥ 60	8 (26.7%)	11 (36.7%)	
Smoking	Yes	15 (50.0%)	12 (40.0%)	0.436
	No	15 (50.0%)	18 (60.0%)	
Diabetes mellitus	Yes	12 (40.0%)	17 (56.7%)	0.196
	No	18 (60.0%)	13 (43.3%)	
Hypertension	Yes	15 (50.0%)	13 (43.3%)	0.605
	No	15 (50.0%)	17 (56.7%)	
Deep vein thrombosis (DVT)	Yes	17 (56.7%)	15 (50.0%)	0.605
	No	13 (43.3%)	15 (50.0%)	

participants in the pentoxifylline group were between 40 and 59 years old. The participants under 40 years old were lower in both groups. However, the pentoxifylline group had a higher prevalence of participants over 60 (36.7%) compared to the aspirin group (26.7%).

The Shapiro-Wilk test was used to assess the normality of several variables related to chronic leg ulcers and associated factors (e.g., age, BMI, ulcer size, pain score) across different time points as shown in **Table 1**. The p-values from the Shapiro-Wilk test indicate whether each variable follows a normal distribution. All variables (age, BMI, ulcer size, pain score) failed the Shapiro-Wilk test with p-values less than 0.05, indicating that they do not follow a normal distribution.

Overall, the distributions of the two groups were generally similar in terms of key clinical risk factors, demographic characteristics, and BMI categorization. The statistical analysis of the study reveals that there were no significant differences between the two groups (Oral Aspirin and Oral Pentoxifylline) on several variables. As presented in the **Table 1**. For continuous variables, the Mann-Whitney U test was used to compare differences between the groups, while for categorical variables, the Chi-square test was employed. Overall, the results suggest that there are no significant differences between the two treatments (Oral Aspirin and Oral Pentoxifylline) across these clinical and demographic variables.

The Effect of oral aspirin and pentoxifylline on ulcer size reduction and pain scores from baseline to follow-up are depicted in **Table 2**. The number of lesions (1.50±0.51 vs. 1.57±0.50) and ulcer duration (2.78±1.29 vs. 2.61±1.37 months; p=.657) were not significantly different within the aspirin and pentoxifylline groups as confirmed by the Mann-Whitney U test. The statistical analysis (Mann-Whitney U test) also revealed non-significant (p>0.05) difference for the number of lesions showed by both groups. This indicates that both groups had a similar distribution of lesion counts. The Aspirin group displayed a relatively equal distribution of ulcers on the leg (32.30%) and foot (32.30%), with a slightly higher proportion (35.50%) of multiple ulcers. Conversely, the Pentoxifylline group had a higher proportion of foot ulcers (45.20%) compared to the leg (25.80%) and a lower proportion of multiple sites (29.00%).

Table 2 Effect of oral aspirin and pentoxifylline on ulcer size reduction and pain scores from baseline to follow-up.

Variable	*Aspirin (n=30) Mean ± SD*	*Pentoxifylline (n=30) Mean ± SD*	*P-values*
Duration of ulcer (months)	2.78±1.29	2.61±1.37	0.657
No. of lesions	2±1	2±1	0.608
Site Of Ulcer (Leg)	10(32.30%)	8(25.80%)	0.722
Site Of Ulcer (Foot)	10(32.30%)	14(45.20%)	
Site Of Ulcer (Multiple)	11(35.50%)	9(29.00%)	
Ulcer size (cm²) - baseline	10.30±6.30	7.67±8.52	0.005
Ulcer size (cm²) - 1 month	6.33 ± 2.06	3.73±3.68	0.001
Ulcer size (cm²) - 2 months	2.70 ± 2.07	1.67±1.15	0.301
Ulcer size (cm²)- 3 months	1.30±0.47	0.80±0.48	0.001
Pain score - baseline	6.53±3.25	6.17±3.50	0.789
Pain score - 1 month	4.57±1.79	3.60±2.08	0.062
Pain score - 2 months	2.40±1.00	1.73±0.87	0.007
Pain score - 3 months	0.97±0.61	0.80±0.61	0.293

The Chi-square test showed that there is no significant difference in the site of ulcer distribution (leg, foot, or multiple) between the two groups (p>0.05), suggesting a similar distribution of ulcer sites across both groups.

At baseline, the ulcer size was larger in the aspirin group (10.30 cm²) than in the pentoxifylline group (7.67 cm²), with a significant difference between the groups (p>0.005). Both groups displayed a decrease in ulcer size at one month. The Pentoxifylline group's reduction was significantly larger (3.73±3.68cm²) than the Aspirin group's (6.33±2.06cm²), with a p-value of .001. However, after two months difference in ulcer size across groups was non-significant (p=.301; aspirin: 2.70±2.07cm²; pentoxifylline: 1.67±1.15cm²). Contrarily, after three months, both medicines exhibited significantly decreased size of ulcers as shown in the **Figure 1**. Nevertheless, Pentoxifylline demonstrated a larger reduction (0.80±0.48cm²) than Aspirin (1.30±0.47cm²) as mentioned in the **Table 2**. Patients on pentoxifylline observed a more substantial and long-lasting reduction in ulcer size.

At baseline, the aspirin group's pain score was 6.53±3.25, while the pentoxifylline group was 6.17±3.50 with a p-value of 0.789, showing no significant difference as presented in the **Table 2**. The pentoxifylline group had a reduced pain score after one month, but this difference was not significant (3.60±2.08 vs. 4.57±1.79;). At two months, the pentoxifylline group showed a statistically significant decrease in pain when compared to the aspirin group (1.73±0.87 vs. 2.40±1.00). After three months, pain score was minimal in both groups (0.80±0.61 vs. 0.97±0.61).

Additionally, the Mann-Whitney U test demonstrated that pentoxifylline reduced both ulcer size and pain scores more than aspirin, particularly during one and three months. At two months, there were no obvious distinctions between the two treatments' effects.

The analysis showed that none of the groups had any adverse events such as neurological, gastrointestinal, bleeding-related, or other systemic symptoms at the start of the trial as depicted in the **Figure 2**. Participants using oral aspirin reported five (16.7%) adverse events after a month, whereas those taking

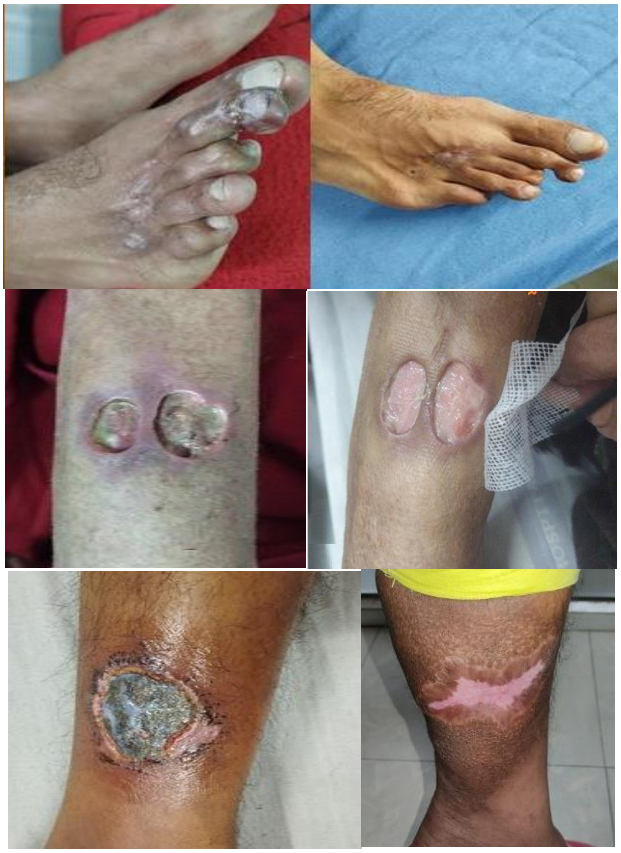

Figure 1 Wound appearance before (left-column) and after treatment (right-column) showing ulcer size improvement.

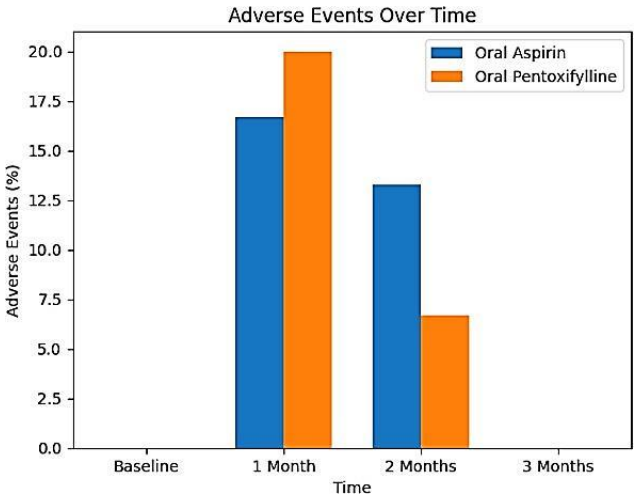

Figure 2 Safety profile of oral aspirin and oral pentoxifylline as assessed by reported adverse events at baseline and follow-up visits.

oral pentoxifylline reported seven (23.3%) adverse events, this difference was not statistically significant (p>.05; Fisher's exact test). Adverse events reduced in both groups following two months, with 4 out of 30 patients (13.3%) in the aspirin group and 1 out of 30 patients (3.3%) in the pentoxifylline group. After three months, no adverse events were observed in either group. Overall, adverse events were infrequent and did not differ significantly between treatment groups at any assessed time point. Overall, the two treatments demonstrated a similar safety profile throughout the study. However, oral pentoxifylline was more effective than oral aspirin at reducing the size of ulcers over time, with faster and more noticeable outcomes as well as a greater reduction in pain over the intermediate follow-up period.

Discussion

The current trial demonstrated the safety and efficacy of oral aspirin and pentoxifylline for chronic leg ulcers treatment. Both the aspirin and pentoxifylline groups had similar baseline demographics and clinical risk factors, such as BMI, gender, age distribution, smoking status, presence of diabetes mellitus, hypertension, and deep vein thrombosis. Similarly, there were no significance variations in the initial ulcer such as the number of lesions, ulcer length, and baseline ulcer size, indicating a well-balanced randomization that enables direct comparison of treatment effects. Over the period of three-month follow-up, oral pentoxifylline exhibited higher efficacy in improving ulcer healing and lowering its associated pain. The substantial difference in ulcer size reduction observed in this study is a notable finding. At one, two, and three months after intervention, the pentoxifylline group's ulcer size decreased substantially faster than that of the aspirin group indicated that pentoxifylline not only promotes faster ulcer healing but also associated with ulcer size reduction. This is consistent with the previously reported researches that pentoxifylline help cure wounds, especially venous leg ulcers.[1,2] The pentoxifylline's evidence reported better effectiveness align with systematic reviews and randomized controlled studies.[4]

Jull *et al*.[13] reported that pentoxifylline substantially enhances the healing of venous leg ulcers, given either as a substitute to compression therapy or to patient who are unable to tolerate compression, compared with placebo. These findings have been further supported by meta- analyses. According to Sun *et al*.[17] pentoxifylline significantly improved ulcer healing rates, overall clinical improvement, and healing length. The data supporting pentoxifylline as an effective alternative therapy for VLUs was most recently confirmed by Salih *et al*;[19] who observed a considerable increase in complete ulcer healing rates when compared with controls (OR=2.56, 95% CI 1.97–3.32).

In contrast, studies evaluating aspirin on venous leg ulcers produced inconsistent results. Pilot controlled studies have consistently revealed no significant advantage over placebo as an addition for traditional therapy, although some earlier research demonstrating that low-dose aspirin might improve healing time.[15] Low therapeutic efficacy observed in the present study could be due to multiple reasons such as suboptimal dosing, a 12-week follow-up period and small sample size. In comparison to broader hemorheological agents, aspirin primarily inhibits platelet aggregation via cyclooxygenase-1

suppression, but this mechanism may not sufficiently target the underlying microcirculatory impairment and persistent inflammation involved in chronic leg ulcers.[15-17,21]

Pentoxifylline is a hemorheological substance that has been shown to reduce blood viscosity, platelet aggregation, and fibrinogen levels, promote erythrocyte flexibility, and enhance microcirculatory blood flow and oxygenation of ischaemic tissues.[13] These mechanisms, including improved tissue circulation and reduced inflammation may account for the greater efficacy in promoting ulcer healing.[21]

Furthermore, pentoxifylline's anti-inflammatory effects may reduce the production of pro-inflammatory cytokines i.e., interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), subsequently lead to poor wound healing and long-term tissue damage[17] The complex mechanism, including increased fibrinolysis, reduced inflammation, and improved perfusion, combine to develop an environment that promotes the growth of granulation tissue and epithelialisation. This indicates a faster decrease in ulcer size was noticed by the pentoxifylline group.[22] Venous ulcer healing due to aspirin's antiplatelet activity through irreversible inhibition of cyclooxygenase-1, which suppress thromboxane A_2–mediated platelet aggregation. This mechanism may improve microcirculatory blood flow, reduce microthrombus formation, and helps to modulate haemostatic abnormalities linked with chronic venous insufficiency.[20] However, aspirin lacks the hemorheological and anti-inflammatory effects noted with pentoxifylline, including enhanced fibrinolysis and improved erythrocyte deformability. This limited range of action may explain the lower efficacy of aspirin compared with pentoxifylline observed in the present trial. The results of our study also demonstrate that aspirin is less effective as compare to pentoxifylline in pain and ulcer size reduction.

These findings further suggest that aspirin may have a limited effect in ulcer healing in contrast to agents that specifically improve microcirculation. The reduction in pain at one month showed a strong trend toward significance in the pentoxifylline group **(Table 2)**. Moreover, patients with pentoxifylline reported a statistically significant reduction in pain after two months as compared to those receiving aspirin. The overall pattern of pain reduction suggests that pentoxifylline provides more effective medium-term relief from discomfort caused by chronic leg ulcers.[16]

The observed pain reduction in pentoxifylline is most likely explained by its effects on microcirculation and inflammation within the ulcer bed. Pentoxifylline could lower ischaemic nociception associated with chronic ulcers through improving tissue perfusion and oxygenation and lowering pro-inflammatory cytokines and mediators that stimulate nociceptors.[17,23] It is suggested to envision the effect of pain reduction as an indirect result of better wound healing rather than a direct analgesic impact because pentoxifylline lacks inherent analgesic property.[23] During the study period there were no statistically significant variation observed in the incidence of adverse events between the aspirin and pentoxifylline groups.

Over the duration of three-month follow-up, both therapies were usually well tolerated, with few and self-limiting adverse effects. Notably, pentoxifylline did not show greater risk of adverse effects than aspirin, despite greater affectivity. This conclusion is in conformity with earlier research revealing that the most often reported side effects of pentoxifylline are gastrointestinal disorders, which are also moderate and acceptable.[2,13]

Conclusively, this research strengthens the bank of evidence which supports pentoxifylline as a superior pharmacologic agent for the prevention of chronic leg ulcers. It displayed great safety regarding adverse effects, capacity to decrease ulcer size and discomfort considerably.

Conclusion

This study showed that oral pentoxifylline (400 mg twice daily) was more effective than aspirin in reducing ulcer size and pain in patients with chronic

leg ulcers. The results of this study say that pentoxifylline helps wounds heal faster and is just as safe to use as aspirin. Pentoxifylline is good for blood flow and reducing swelling so it might be a choice for treating chronic leg ulcers. Future multicenter studies with longer follow- up periods are needed to evaluate its role in recurrence prevention, quality of life improvement, and health economics.

Declaration of patient consent Authors certify that they have obtained all appropriate patient consent.

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Conflict of interest No conflict of interest.

Author's contribution

TK,MA: Substantial contribution to conception and design, acquisition of data, management of the case, manuscript writing and critical review of the manuscript. Has given final approval of the manuscript version to be published and agreed to be accountable for all aspects of the work.

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