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Original Research Article

Pentoxifylline's Impact on Venous Ulcers: A Randomized Study

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Abstract:

Background: Venous ulcers, a manifestation of chronic venous insufficiency, significantly impact patients' quality of life and pose a burden on healthcare systems. Pentoxifylline, a methylxanthine derivative known for its vasodilatory action, has shown promise in improving microcirculation, reducing inflammation, and enhancing tissue oxygenation, which are critical in the healing process of venous ulcers. The purpose of this research is to assess pentoxifylline's safety and effectiveness in the management of venous ulcers, with an emphasis on healing rates, ulcer size reduction, pain alleviation, and quality of life enhancement.

Methods: A total of sixty individuals with confirmed cases of venous ulcers were enrolled and randomly allotted to one of two groups: the pentoxifylline-treated therapy group or the routine wound care group. Following a baseline, data on healing rates, ulcer size, pain scores, and quality of life were gathered every week. Statistical analysis was accomplished with a significance level of $p < 0.05$.

Results: There were sixty participants in the trial, equally divided between the treatment and control groups. In comparison to the control group, the pentoxifylline group demonstrated a considerably higher healing rate (80% vs. 50%, $p < 0.05$) and a bigger reduction in ulcer size (65% vs. 45%, $p < 0.01$). The pentoxifylline group also experienced a significant improvement in pain scores and quality of life indicators. The fact that no significant side effects were recorded suggests the safety of the medication.

Conclusion: Pentoxifylline significantly enhances the healing of venous ulcers, reduces pain, and improves the quality of life in patients, with minimal side effects. Its use as an adjunct to standard wound care offers a promising approach to managing this challenging condition.

Recommendations: Future research should focus on long-term outcomes of pentoxifylline treatment and its integration into comprehensive venous ulcer management protocols. Larger, multicentric trials are recommended to validate these findings and explore the full potential of pentoxifylline in venous ulcer care.

Keywords: Pentoxifylline, Venous Ulcers, Wound Healing, Quality of Life.

Introduction

Pentoxifylline, a methylxanthine derivative, has been increasingly recognized for its therapeutic effects beyond its primary use as a vasodilator. Its impact on venous ulcers, a chronic and often debilitating condition, has garnered significant attention within the medical community. Venous ulcers, stemming from venous insufficiency, represent a substantial burden on healthcare systems and significantly impair patients' quality of life. The pathophysiology of venous ulcers involves a complex interplay of hemodynamic changes, inflammation, and cellular dysfunction, leading to impaired wound healing [1].

Pentoxifylline's mechanism of action is multifaceted, offering benefits that extend to the microcirculatory level, which is crucial in the context of venous ulcers. It improves blood flow, reduces blood viscosity, and has anti-inflammatory properties, all of which are beneficial in enhancing tissue oxygenation and promoting ulcer healing [2]. Clinical trials and studies have demonstrated that pentoxifylline, either as monotherapy or in conjunction with compression therapy, significantly improves the healing rates of venous ulcers compared to placebo or compression therapy alone [3].

The efficacy of pentoxifylline in treating venous ulcers can be attributed to its ability to modulate leukocyte activity, decrease the production of tumor necrosis factor-alpha (TNF-α), and reduce the concentration of fibrinogen, thereby improving microcirculatory flow and reducing the inflammatory response that impedes healing [4]. Furthermore, pentoxifylline has been shown to enhance fibroblast growth and collagen synthesis, essential processes in wound repair [5].

The study aims to investigate the efficacy and safety of pentoxifylline in the treatment of venous ulcers, with a focus on assessing its impact on ulcer healing rates, reduction of ulcer size, pain relief, and improvement in overall patient quality of life.

Methodology

Study Design: A randomized controlled trial design.

Study Setting: The study was carried out at Indira Gandhi Institute of Medical Science (I.G.I.M.S), Patna, Bihar, India, between July 2020 to December 2020.

Participants: A total of 60 participants were enrolled in the study. Participants were recruited from the hospital's outpatient wound care clinic.

Inclusion Criteria:

1. Adults aged 18 years and above.

2. Diagnosed with venous ulcers.

3. Willing to provide informed consent for participation.

Exclusion Criteria:

1. Presence of arterial ulcers.

2. History of hypersensitivity to pentoxifylline.

3. Pregnancy or breastfeeding.

4. Uncontrolled diabetes mellitus.

5. Concurrent use of medications known to interfere with wound healing.

Bias: Efforts were made to minimize bias through randomization of participants into treatment and control groups, blinding of assessors during outcome assessment, and maintaining consistency in data collection procedures.

Variables: Variables included administration of pentoxifylline, venous ulcer healing rates, reduction in ulcer size, pain scores, and quality of life measures.

Data Collection: Data on participant demographics, medical history, and ulcer characteristics were collected at baseline. Weekly assessments were conducted to measure ulcer healing rates, reduction in ulcer size, and pain scores. Quality of life measures were assessed at the beginning and end of the study.

Procedure: Participants meeting the inclusion criteria were randomized into either the treatment group receiving pentoxifylline or the control group receiving standard wound care. Pentoxifylline was administered orally according to standard dosing guidelines. All participants received standard wound care including compression therapy and wound dressings. Weekly follow-up visits were scheduled for assessment and data collection.

Statistical Analysis: Software for statistics was used to analyse the data (SPSS version 20.0). Results and participant characteristics were summarised using descriptive statistics. The study utilised inferential statistics, such as ANOVA and t-tests, to compare the results obtained by the treatment and control groups. The threshold for significance was $p < 0.05$.

Ethical Considerations: The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Result

Sixty participants were enrolled in the study, with 30 participants allocated to the pentoxifylline treatment group and 30 participants allocated to the control group. The mean age of participants was 55 years (± 8.2), with a majority being female (60%). Baseline characteristics, including ulcer size, duration, and pain scores, were similar amongst the two groups, ensuring comparability at the outset of the study.

Table 1: Demographic profile

Characteristic	Pentoxifylline Group (n=30)	Control Group (n=30)
Age (years), Mean	56.2 (± 8.5)	54.8 (± 7.9)
Gender, n (%)		
- Male	12 (40.0%)	15 (50.0%)
- Female	18 (60.0%)	15 (50.0%)
Ulcer Size (cm²), Mean	8.7 (± 3.2)	8.9 (± 3.5)
Ulcer Duration (weeks), Mean	14.6 (± 6.3)	13.8 (± 5.9)
Comorbidities, n (%)		
- Hypertension	9 (30.0%)	11 (36.7%)
- Diabetes Mellitus	7 (23.3%)	6 (20.0%)
- Obesity	6 (20.0%)	8 (26.7%)
- Others	8 (26.7%)	5 (16.7%)

The pentoxifylline treatment group demonstrated a significantly higher rate of venous ulcer healing compared with the control group ($p < 0.05$). By the end of the study period, 80% of participants in the pentoxifylline group achieved complete ulcer healing, whereas only 50% of participants in the control group experienced complete healing.

Participants receiving pentoxifylline demonstrated a greater reduction in ulcer size as compared with the control group. The pentoxifylline group saw an average decrease in ulcer size of 65% (± 12%) over the trial, compared to a mean decrease of 45% (± 8%) in the control group. There was a statistically significant difference ($p < 0.01$).

Table 2: Outcome measures

Outcome Measure	Pentoxifylline Group	Control Group	p-value
Venous Ulcer Healing Rate (%)	80	50	<0.05
Reduction in Ulcer Size (%)	65 (±12)	45 (±8)	<0.01
Pain Score Reduction	4 (±1.5)	2 (±1)	<0.001
Patient Compliance (%)	95	92	-
Time to Ulcer Healing (weeks)	8 (±2)	12 (±3)	<0.001
Recurrence Rate (%)	10	30	<0.01

A visual analogue scale (VAS) was used to measure pain, and the pentoxifylline group's scores significantly improved in comparison to the control group. The pentoxifylline group's participants reported an average decrease in their pain scores of 4 points (± 1.5), while the control group's participants reported an average reduction of 2 points (± 1). There was a statistically significant difference ($p < 0.001$).

Quality of life measures, assessed using standardized questionnaires such as the SF-36, showed a significant improvement in the pentoxifylline group with comparison to the control group. Participants receiving pentoxifylline reported higher scores in domains related to physical functioning, pain, and overall well-being ($p < 0.05$).

No serious adverse events related to pentoxifylline were reported during the study period. Mild gastrointestinal symptoms such as nausea and dyspepsia were reported by a small proportion of participants in both groups, but these were transient and did not necessitate discontinuation of treatment.

Discussion

The study's findings show that pentoxifylline significantly improves the course of venous ulcer therapy. With 80% of patients attaining complete ulcer healing compared to only 50% in the control group, the pentoxifylline group had a considerably greater rate of venous ulcer healing. This shows that pentoxifylline speeds up the venous ulcer healing process.

Furthermore, in comparison with those in the control group, pentoxifylline recipients showed a larger reduction in ulcer size. During the course of the trial, the pentoxifylline group experienced an average decrease in ulcer size of 65%, compared to a mere 45% in the control group. This suggests that pentoxifylline helps to both accelerate healing and significantly reduce the size of venous ulcers.

In addition, the pentoxifylline group's pain scores considerably decreased in compared to the control group. The pentoxifylline group's participants reported an average 4-point decrease in pain levels, suggesting a significant improvement in venous ulcer discomfort. For patients with venous ulcers to have a better overall quality of life and general well-being, pain management must improve.

Moreover, quality of life measures, including physical functioning, pain, and overall well-being, were significantly better in the pentoxifylline group compared to the control group. This suggests that pentoxifylline not only improves clinical outcomes but also enhances the subjective experience and functional status of patients with venous ulcers.

Importantly, the study found no serious adverse events related to pentoxifylline, indicating its safety profile and suitability for use in the treatment of venous ulcers. This is crucial information for clinicians considering the use of pentoxifylline as an adjunctive therapy for venous ulcers, as it provides reassurance regarding its safety and tolerability.

The management and treatment of venous ulcers encompass a range of approaches, from clinical evaluations to the exploration of various therapeutic interventions. Studies on Pentoxifylline's impact on venous ulcers offers valuable insights into the broader management strategies and challenges associated with venous ulcers.

Evidence supports the use of oral pentoxifylline, preferably alongside compression therapy, as an effective management strategy for venous leg ulceration. This combination has been shown to improve healing outcomes compared to compression therapy alone [6].

Current guidelines also endorse the treatment of venous ulcers with a multifaceted approach that includes compression therapy, exercise, dressings, and pentoxifylline. This all-encompassing approach is advised for ulcers that are substantial, persistent, or resistant to conservative treatment, highlighting the significance of pentoxifylline in the therapeutic arsenal [7].

One significant study conducted of Eastern India focused on the clinico-etiological evaluation of chronic leg ulcers (CLUs), identifying venous ulcers and mixed ulcers as the most common types among patients. This study underscores the incidence and complexity of managing venous ulcers in the region, highlighting the need for effective treatment modalities [8].

The medical management of venous ulcers involves a comprehensive approach, including lifestyle modifications and the use of compression garments. These strategies aim to control edema and improve venous circulation, which are crucial for the healing of venous ulcers. Such management techniques provide a context for understanding how pharmacological interventions like Pentoxifylline could be integrated into treatment plans to enhance outcomes [9].

A broader perspective on venous ulcer treatment is provided by a study that reviews current evidence supporting various interventions, including compression therapy, exercise, dressings, and Pentoxifylline. This study emphasizes the multifaceted nature of venous ulcer management and the importance of adopting a comprehensive treatment strategy to address the condition effectively [10].

Another crucial component of patient care is the psychosocial effects of persistent foot and leg ulcers. Examining the impact of bibliotherapy on patients with chronic ulcers' quality of life, distress, and depression indicates that psychosocial aspects of ulcer management must be addressed. This approach can complement pharmacological treatments by reducing the mental health burden associated with chronic physical illnesses, thereby potentially improving overall treatment outcomes [11].

The role of compression therapy in managing chronic venous insufficiency, which often leads to venous ulcers, is highlighted in research discussing the state of art in inflammation and compression. This study reinforces the consensus that strong compression pressure is more efficient than low compression pressure in promoting ulcer healing, setting a foundation for integrating other treatments like Pentoxifylline to optimize healing processes [12].

Conclusion

The results of the study display that pentoxifylline is effective in promoting venous ulcer healing, reducing ulcer size, relieving pain, and improving the quality of life of patients. These findings support the use of pentoxifylline as a valuable adjunctive therapy in the management of venous ulcers, offering potential benefits for patients and healthcare providers alike.

Limitations: The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation: Future research should focus on long-term outcomes of pentoxifylline treatment and its integration into comprehensive venous ulcer management protocols. Larger, multicentric trials are recommended to validate these findings and explore the full potential of pentoxifylline in venous ulcer care.

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List of Abbreviations:

TNF-α: tumor necrosis factor-alpha

VAS: visual analogue scale

CLU: chronic leg ulcers

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References

1. Chi YW, Raffetto JD. Venous leg ulceration pathophysiology and evidence based treatment. Vascular Medicine. 2015 Apr;20(2):168-81.
2. Jones JE, Nelson EA. Skin grafting for venous leg ulcers. Cochrane Database of Systematic Reviews. 2007(2).
3. Carvalho MR, Silveira IA, Oliveira BG. Treatment of venous ulcers with growth factors: systematic review and meta-analysis. Revista brasileira de enfermagem. 2019 Jan;72: 200-10.
4. Dale JJ, Ruckley CV, Harper DR, Gibson B, Nelson EA, Prescott RJ. Randomised, double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. Bmj. 1999 Oct 2;319(7214):875-8.
5. McCarty MF, O'Keefe JH, DiNicolantonio JJ. Pentoxifylline for vascular health: a brief review of the literature. Open heart. 2016 Feb 1; 3(1):e000365.
6. Adderley U. Prescribing for the management of venous leg ulceration. Nurse Prescribing. 2015;13(8):380-383.
7. Millan SB, Gan R, Townsend PE. Venous ulcers: diagnosis and treatment. American family physician. 2019 Sep 1;100(5):298-305.
8. Chen L, Gao Y, Liu M, et al. Efficacy and safety of pentoxifylline for chronic venous leg ulcers: study protocol for a multicenter randomized controlled trial in China (ESPECT study). Trials. 2023;24(1):491. Published 2023 Aug 2.
9. Nag F, Chatterjee G, Ghosh A, De A. Clinico-Etiological Evaluation of Chronic Leg Ulcer in a Tertiary Care Center of Eastern India. Indian J Dermatol. 2020;65(6):495-499. doi:10.4103/ijd.IJD_62_20.
10. Pascarella L, Shortell CK. Medical management of venous ulcers. Semin Vasc Surg. 2015;28(1):21-28. doi:10.1053/j.semvascsurg.2015.06.001.
11. Kirupa P, Shrinivasa Bhat. Effectiveness of bibliotherapy on quality of life, distress and depression among chronic leg and foot ulcer. Int J Health Sci Res. 2021;11(4):93-101.
12. Ligi D, Croce L, Mannello F. Inflammation and compression: the state of art. Veins and Lymphatics. 2016 Jun 14;5(1).