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Original Article

Surgery Section

Pentoxifylline: A New Armamentarium in Diabetic Foot Ulcers

VENKATESH REWALE[1], KIRAN RAVI PRABHAKAR[2], ANJALI M. CHITALE[3]

ABSTRACT

Background: Diabetic foot ulcers are estimated to affect 15% of all diabetics and precede almost 85% of foot amputations. Pentoxyfylline a substituted xanthenes' derivative has been reported to increase the blood flow to the microcirculation and enhances tissue oxygenation. It has been widely used in the treatment of intermittent claudication.

Materials and Methods: Pentoxyfylline is known to decrease the rouleaux formation of RBC and hence helps in improving the microcirculation. Out of 67 patients 30 received pentoxyfylline and 32 were on traditional treatment and there was loss of follow-up in five cases.

The response was observed subjectively, histologically and by Doppler studies.

Results: It was observed that the patients on pentoxyfylline had early healing as compared to patients receiving only conventional treatment as evident on biopsy and Doppler.

Conclusion: Here in this research our objective was to determine whether pentoxyfylline (trental 400 mg) taken orally TDS in addition to ambulatory compression bandages and dressings improves the healing rates of diabetic ulcers.

Keywords: Pentoxyfylline, Doppler study, Diabetic foot ulcers

INTRODUCTION

Diabetes mellitus is recognized as an epidemic in asian sub continent affecting 25 millions in india alone [1,2].

Diabetic foot ulcer is one of the significant complications of diabetes mellitus [3,4]. Diabetic foot ulcers are estimated to affect 15 % of all diabetics and precede almost 85 % of foot amputations [5,6].

The four main causes for development of diabetic foot ulcers are peripheral neuropathy [7,8], peripheral vascular disease [9,10], charcot foot [11] & infection.

Pentoxyfylline is a xanthenes' derivative which decreases blood viscosity, increases RBC flexibility, increases blood flow to microcirculation thus enhancing tissue oxygenation and thereby reducing leukocyte adhesion. It is also mild fibrinoytic and is thus effective in venous leg ulcers [12].

Pentoxyfylline is known to decrease the rouleaux formation of RBC & hence helps in improving the microcirculation [13]. It has been widely used in the treatment of intermittent claudication [14].

This study was undertaken to evaluate the efficacy of pentoxyfylline 400 mg (trental 400 mg) in patients with strictly defined ulcers.

The primary objective of this study was to determine whether pentoxyfylline 400 mg taken orally TDS for 30 days in addition to traditional treatment improves healing in diabetic foot ulcers.

AIMS AND OBJECTIVES

1. To assess the effectiveness of pentoxyfylline as an adjuvant to routine treatment in patients with diabetic foot ulcer.
2. To assess the effect of pentoxyfylline on vascularity and marginal blood velocity in patients with diabetic foot ulcer.
3. To assess the effect of pentoxyfylline on ulcer healing in patients with diabetic foot ulcer and compare it with control group.

MATERIALS AND METHODS

- Out of total 67 patients, two identical groups were formed, Group A (patients who received only traditional treatment, i.e., bed rest with elevation, i.e., antibiotics, analgesics and dressings) and Group B (patients who received pentoxyfylline along with traditional treatment).
- Group B (30 patients) received pentoxyfylline together with traditional treatment and Group A (32 patients) received only traditional treatment. There was loss of follow-up in five cases.

The effect of pentoxyfylline on vascularity and marginal blood velocity in patients with diabetic foot ulcer was assessed in the beginning and at the end of 30 days. This was achieved by a base line biopsy from the edge of diabetic ulcer and marginal blood flow velocity measurement by means of Doppler and after 30 days of administration of pentoxyfylline. The response was observed subjectively, objectively, on histological basis, visually and by Doppler.

The following inclusion/exclusion criteria were used for recruitment of patients in the study:

Inclusion Criteria

The patients admitted in the (Inner Patient Department) IPD with diabetic foot ulcer with Wegner's grading.

Grade 0, 1, 2, with no other systemic complications.

Exclusion Criteria

Critically ill patients or patients with the systemic disease and patients with diabetic foot ulcer with Grade 3,4,5.

After 30 days of treatment patients were reassessed by edge biopsy.

Mean velocity in the patients treated with pentoxyfylline was 26.73±3.55 (Group B) and that of other patients were 25.66±3.12 (Group A) the difference was not significant [Table/Fig-1].

However the mean improvement in blood velocity in the patients treated with pentoxyfylline was 0.21± 0.03 and that of other patients were 0.09 ± 0.04 [Table/Fig-1].

Thus the difference was statistically significant.

This indicates that pentoxyfylline increases blood flow significantly.

	Parameter	Group B	Group A	p-value
1	Doppler velocity pre-treatment	26.73±3.55	25.66±3.12	0.21
2	Doppler blood velocity post-treatment	0.21±0.03	0.09±0.04	0.001

[Table/Fig-1]: Effect on blood velocity by Doppler in two groups

Mean follow up in the patients treated with pentoxyfylline was 32.19 ± 13.22 and that of other patients were 38.17 ± 14.00. This indicates that pentoxyfylline does not reduce the follow up timing.

Wound Biopsy on Day 30	No of Patients		p-value
	Group B	Group A	
Signs of recovery	26 (86.66%)	20 (62.5%)	0.05
Signs of inflammation	04 (13.33%)	12 (37.5%)	

[Table/Fig-2]: Effect of pentoxyfylline on wound healing
Chi-square test is applied. P value is significant if it is less than 0.05

- In Group B, i.e., patients treated with pentoxyfylline out of the 30 Patients who came for follow up on day 30, 26 (86.66%) showed the signs of ulcer recovery while only 04 (13.33%) patients showed the signs of inflammation [Table/Fig-2].
- However in Group A in 32 patients treated with traditional treatment and who came for follow up on day 30, only 20 (62.5%) patients showed the signs of ulcer recovery while 12 (37.5%) showed the signs of inflammation [Table/Fig-2].

Thus the difference was statistically significant as this signifies that the patients treated with pentoxyfylline showed good improvement in healing as compared to patients who received no treatment.

Improvement>10 x 10 mm on Day 30	No of Patients		p-value
	Group B	Group A	
YES	23 (76.66%)	17 (53.12%)	0.09
NO	7 (23.33%)	15 (46.87%)	

[Table/Fig-3]: Effect of Pentoxyfylline on wound healing (Improvement >10 x 10mm) Chi-square test is applied. p-value is significant if it is less than 0.05.

- In 30 patients who came for follow up on day 30, 23 (76.66%) patients treated with pentoxyfylline showed improvement >10x10 mm on day 30 while 07 (23.33%) patients showed less improvement [Table/Fig-3].

In other group treated traditionally, 32 patients came for follow up on day 30, 17 (53.12%) patients showed improvement >10x10 mm on day 30 while 15 (46.87%) showed less improvement [Table/Fig-3].

This signifies that the patients treated with pentoxyfylline showed improvement in healing.

Blood Velocity

In our study we observed the pentoxyfylline had effect on velocity of blood flow and the drug increases blood flow to ulcer area. Study result shows that mean velocity in the patients treated with pentoxyfylline was 26.73±3.55 and that of other patients were 25.66±3.12. Though the mean velocity of blood flow was higher in patients with pentoxyfylline group the difference was not significant mean improvement in blood velocity in the patients treated with pentoxyfylline was 0.21±0.03 and that of other patients were 0.09±0.04 the difference was statistically significant; indicating that pentoxyfylline increases blood flow significantly [Table/Fig-1].

Presence of slough	No of patients		p-value
	Group B	Group A	
YES	22 (73.33%)	14 (43.75%)	0.03
NO	08 (26.66%)	18 (56.25%)	

[Table/Fig-4]: Effect of Pentoxifylline on presence of slough
Chi-square test is applied. p-value is significant if it is less than 0.05.

In 30 patients, who came for follow up on day 30, 22(73.33 %) patents from Group B, i.e., treated with pentoxyfylline showed the presence of minimal slough on day 30.

While 08 (26.66 %) showed no slough.

In other Group i.e., Group A in 32 patients who came for follow up on day 30, 14 (43.75 %) patients showed the presence of minimal slough. While 18 (56.25 %) showed no slough [Table/Fig-4].

The difference was statistically significant.

This signifies that the patients treated with pentoxyfylline showed good improvement in healing as compared to patients who received only traditional Treatment.

DISCUSSION

As observed earlier foot ulcers are estimated to affect 15% to 25% of all diabetics during their lifetime. Foot ulcers also precede almost 85% of all foot amputations. The management of diabetic foot ulcers is mainly into three parts: removal of callus, treatment and eradication of infection and reduction of weight bearing forces by bed rest. It has been shown that neuropathy and ischemia are the principal disorders underlying foot problems. Thus, management of foot ulcer is largely determined by its severity, vascularity & the presence of infection.

Wagner (1983) has described a grading system for the foot lesion from 0-5 by observing the depth and extent of the ulcers [15].

Grade	Description
0	No ulcer but high risk foot
1	Superficial Ulcer (commonest site is head of 1st metatarsal)
2	Deep ulcer with no bony involvement
3	Abscess with bony involvement
4	Localised gangrene
5	Gangrene of whole foot

Ulcer Grade

As planned earlier, the study enrolled only patients with Grade 1 and Grade 2 ulcers, In majority of the patients 40 (59.70%), Grade 2 ulcer was present and in 26 (38.81%) patients Grade 1 ulcer was present. Out of 67 patients studied 11 (16.42%) patients had punched wound, 50 (74.63%) patients had sloping wounds and the remaining 6 patients (8.96%) had vertical wounds out of the 67 patients studied, 6 patients (8.96%) had H floor, 21 patients (31.34%) had P floor 22 patients (32.84%) had S floor 1 patient had S/H floor and the remaining 17 patients (2537%) had S/P floor 30 (44.78%) ulcer were tender and 35 (52.24%) ulcer were non tender data in two patients were missing. majority of patients had grade D+ pulsation, three patients had grade D++ pulse and 25 patients (37.31) had grade P+ pulse.

Mean Follow Up

Mean follow up in the patients treated with pentoxyfylline was 32.19±13.22 and that of other patients were 38.17±14.00. The mean follow up was higher in the patients who received no treatment the difference was not significant. This indicates that pentoxyfylline does not reduce the follow up timing.

Signs of Ulcer Recovery

In our study, 30 patients who came for follow up on day 30, 26 (86.66%) patients treated with pentoxyfylline showed the signs of ulcer recovery while 04 (13.33%) showed the signs of inflammation in other group, in 32 patients came for follow up on day 30, 20 (62.5%) patients showed the signs of ulcer recovery while 12 (37.5%) showed the signs of inflammation [Table/Fig-2]. The difference was statistically significant. This signifies that the patients treated with pentoxyfylline shows good improvement in healing as compared to patients who received no treatment.

Similar findings were also reported by Weitgasser [16]. The author evaluated pentoxyfylline in 70 patients with leg ulcers. The patients

were treated with pentoxyfylline in addition to hitherto applied local therapy. The treatment comprised of two months with daily dosage of 800 mg to 1200 mg. of pentoxyfylline. Weitgasser observed that more than 80% of patients with medium size ulcers get cured by therapy [16].

A similar study was conducted by Ramani et al., [17,18]. In their study 40 diabetic patients with foot ulcers of which 20 of them received conventional therapy and 20 received Pentoxyfylline (400 mg three times a day), after eight weeks healing of ulcers was significantly higher in those who received pentoxyfylline. Ramani found that the administration of pentoxyfylline in addition to conventional therapy was significantly superior in the management of diabetic foot ulcers [17,18].

RESULTS

- Patients treated with pentoxyfylline showed good improvement in healing as compared to patients who did not receive pentoxyfylline.
- Pentoxyfylline increases blood flow significantly.

The result of our study is comparable to parallel study carried out by Weitgasser [16] and Ramani et al., [17,18].

CONCLUSION

- It was observed that the patients on pentoxyfylline had early healing as compared to patients who received only Conventional treatment.

We hope that pentoxyfylline one day would be an established part of the armamentarium in treating diabetic foot ulcer.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of General Surgery, A.C.P. M Medical College, Sakri Road, Dhule, Maharashtra – 424001, India.
2. PG Resident (3rd year), Department of General Surgery, A.C.P.M Medical College, Sakri Road, Dhule, Maharashtra – 424001, India.
3. Professor & Head, Department of General Surgery, A.C.P.M Medical College, Sakri Road, Dhule, Maharashtra – 424001, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kiran R. Prabhakar,
Resident, Department of General Surgery, A.C.P.M Medical College, Sakri Road, Dhule, Maharashtra- 424001, India.
Phone: 09420708996; 09226362201, Email: sandyprabhakar@rediffmail.com

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