Original Article

A PROSPECTIVE STUDY TO COMPARE WOUND HEALING IN DIABETIC FOOT ULCERS IN PATIENTS WITH AND WITHOUT PERIPHERAL VASCULAR OCCLUSIVE DISEASE

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Abstract

Background: There is a high incidence of peripheral vascular occlusive disease (PVOD) in patients with diabetes and this can result in poor outcomes of diabetic foot ulceration (DFU) and wound healing.

Objectives: To compare wound healing in DFU patients with and without PVOD and evaluate differences in wound healing with age and other factors.

Methods: This prospective study enrolled 40 patients with grade 3 (based on Wagner classification) diabetic foot ulcers. Patients with a history of amputation, grade 4 and above ulcers were excluded from the study. based on ankle-brachial index (ABI) values, they were divided into two groups, with and without PVOD. After mapping the initial wound surface area on a graph sheet, wounds were debrided, treated with debriding agents and wound dressing done. All patients were followed once a month for 3 months, each time mapping the progress of wound surface area.

Results: Mean age of patients was 64.05 +/-8.56 (SD). The mean ABI of patients with PVOD was 0.67, while that without PVOD was 1.12 ($p<0.001$). There was no difference in the rate of wound healing between the two groups ($p=0.3487$) and with standard care both sets of patients healed well.

Conclusion: This study did not find any clinically significant difference in the healing of diabetic ulcers with or without PVOD.

Keywords: Ankle-brachial Index, Diabetes, Diabetic Foot, Peripheral Vascular Disease, Wound Healing.

INTRODUCTION

Diabetic foot is an end-stage complication of diabetes mellitus with structural or functional alteration of the foot, that could include ulcerations, infections, or gangrene, which if not treated promptly can result in sepsis requiring amputation. [1] Diabetic foot ulcer (DFU) develops as a result of diabetic neuropathy which causes intrinsic muscle atrophy, and the associated peripheral vascular occlusive disease (PVOD) reducing skin perfusion (1).

DFU has a worldwide prevalence of 6.3% and is rising in India with nearly 11.6% of diabetics suffering from the disease. DFU disproportionately affects patients with type 2 diabetes mellitus (DM) (6.4%) more than type 1 DM (5.5%). (2) Twenty-five per cent of diabetics are susceptible to diabetic foot ulcers during their lifetime. (3) the cornerstone of management is tissue debridement, antibiotics and offloading of the foot (1,4).

Atherosclerosis resulting in PVOD is two to fourfold higher in Diabetes. In addition, PVOD is a predictor of DFU, highlighting the need to evaluate the vascular status of limbs of patients with DFU. (5) Negative outcomes in terms of amputation and mortality rates have been reported in patients with PVOD. (6) A simple cost-effective tool to assess PVOD is the-ankle-brachial index (ABI). ABI is the ratio of systolic blood pressure measured at the ankle to that at the brachial artery (7,8). An ABI ≤ 0.9 indicates PVOD and ≥ 1 rules out PVOD. A lower ABI is indicative of the presence of PVOD. (8,9). Increased calcification at the subintimal plane causes reduced pliability of the arteries, therefore, causing falsely increased ABI >1.2. There is presence of microangiopathy and peripheral neuropathy which also play a major role in the causation of ulcers.

In India, PVOD is prevalent in 29-35% of patients with DFU. (10–12) In non-diabetics, poor healing of foot ulcers is noted in patients with PVOD in comparison to those without PVOD (13,14). The early recognition and treatment of DFU, particularly in patients with PVOD may help improve results. There is a dearth of studies monitoring outcomes in terms of wound healing in DFU patients with PVOD. Our study aimed to compare wound healing in DFU patients with and without PVOD.

METHODS

We conducted a prospective study from June to September 2015 on 40 patients with a confirmed diabetic foot ulcer. The study setting was the General surgery department of a multi-specialty tertiary referral hospital in South India. The study commenced after being approved by the Institutional Human Ethics Committee.

All patients presenting to the general surgery department with grade 3 diabetic foot ulcers based on Wagner classification of diabetic foot ulcers (15) were included in the study. Written informed consent was obtained from all the patients enrolled in the study. Patients with a history of amputation, and grade 4 and above ulcers were excluded from the study.

A total of 40 patients were recruited for this study, between June to September 2015 and were assigned to two groups of 20 patients, after measuring their ankle-brachial index (ABI), (8) using a sphygmomanometer and a handheld Doppler device. Group 1 consisted of patients with an ABI less than 1 and group 2 with ABI greater than or equal to 1. Patients with an ABI score of more than 1.2 or less than 0.5 were excluded (8).

A graph sheet was printed over a transparency sheet to scale, and this was placed over the wound for assessment of the wound area. Standard treatment was provided to both groups, which included daily wound debridement, dressing and pressure offloading. Wounds were dressed using anti-bacterial (Metronidazole 2% -Metrogyl®, JB Chemicals and Pharmaceuticals), anti-fungal (Terbinafine- Daskil®, Novartis India Ltd.), and debridement agent (Papain-urea -Debridace®, Virchow Biotech Ltd.).

All Patients were followed up every three weeks on an outpatient basis and debridement was done when necessary. Swabs/ tissue was sent for culture, and antibiotics were administered according to the sensitivity. The wound surface area was mapped every month for 3 consecutive months. The rate of wound healing was calculated from the difference in wound surface area at the initial presentation and at the third month. Wound healing was obtained from the difference in wound surface area at 1st and 3rd month visits.

Statistical analysis was done using R software version 4.2.1(R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.) and Microsoft Excel. Categorical and continuous variables were represented as frequency, percentage and mean ± standard deviation (SD) / median (minimum, maximum), respectively. The normality of variables was checked by the Shapiro-Wilk test and QQ plot. Two sample t-test was used to compare the mean of variables over groups and the distribution of different variables over groups was done using Mann Whitney U test. Chi-square test was used to assess the dependency between categorical variables. Friedman's test was used to compare the surface area over different time points in both groups. Pairwise Wilcoxon test was used as a post hoc analysis. P-value less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 40 patients with a confirmed diagnosis of diabetic foot ulcer were enrolled for the study and categorized into two groups of 20 each, with and without PVOD, based on ABI. The patients' age ranged between 49-88 years, with a mean (SD) age of 64.05 +/-8.56 years.

Table 1 summarizes the comparison of variables such as age, gender, ABI index, and other comorbidities between both groups. Mean (SD) ABI of patients with PVOD was 0.67 (0.15) and that of patients without PVOD was 1.12 (0.17), which was significantly different between groups ($p<0.001$). The remaining variables like age, gender, and presence of comorbidities were comparable between the groups. A significant number of patients (40%) in the PVOD group underwent Angioplasty ($p=0.0055$).

There was no significant difference in the surface area of wound over consecutive time points, between groups. (Table 2) There was no significant difference in wound healing between groups ($p=0.3487$).

However, using Friedman's test, the surface area of the wound over different time points reduced significantly within both groups ($p<0.001$). Further, from post hoc analysis, there was a significant decrease in the surface area of the wound on comparison at 1st visit with 2nd-month visit ($p= 0.004$) and 3rd-month visit ($p< 0.001$) in those with PVOD. The wound had significantly reduced in size by three months ($p = 0.015$). Similar results were observed in the group without PVOD, where wound surface area at 1st visit was significantly reduced to that at the 2nd-month visit ($p=0.0067$) and 3rd-month visit ($p< 0.001$) in those without PVOD, also at 1st-month visit and 3rd month ($p< 0.001$) in those without PVOD (Table 3).

DISCUSSION

Peripheral vascular occlusive disease is a predictor of poorer outcomes in diabetic foot ulceration. (14) This prospective pilot study compared wound healing in diabetic foot ulcer patients, with or without peripheral vascular occlusive disease.

This study utilized ABI values to confirm the presence of PVOD. The ABI has shown good reliability, along with 89% sensitivity, and 90% specificity to detect PVOD in diabetes and can help as an early screening tool to detect at-risk populations. (16–18) The mean ABI value of patients with PVOD (0.67), in the current study, was significantly lower when compared to those without PVOD (1.12), this indicates a higher risk for cardiovascular events. (7)

In the present study, standard treatment with debridement agents and wound dressing, significantly reduced the wound surface area in both groups. Though clinical wound healing was reduced in PVOD patients when compared to non-PVOD patients, this result did not reach statistical significance. This finding compares to the EURODIALE study which was conducted across 14 diabetic centers in Europe. This study reported a statistically significant reduction in wound surface area with a reported 69% healing rate in patients with peripheral arterial disease, as opposed to 84% healing in those without. (14) Other studies also reported significantly delayed wound healing in patients with PVOD. (19,20) This difference in our finding could be due to a smaller sample size. Further studies need to be conducted on larger population to confirm the diabetic wound healing rates in India.

When wound healing was compared within groups, wound surface area reduced significantly across different time points. Many factors affect the severity and outcomes of DFU like older age, male gender, microbiology of infection, depth and duration of the ulcer itself, and comorbidities such as hypertension. (21) Presence of these factors has also been reported to further increase the risk of PVOD, as observed by lower ABI scores. (9)A recent single-center study conducted in Saudi Arabia reported a higher incidence of coronary artery disease and PVOD in unaffected limb, in patients with vascular aetiology of DFU. (22) In the present study, age, gender, presence of comorbidities such as coronary artery disease, and hypertension did not cause significant differences in wound healing.

LIMITATIONS

The present study had a short follow-up duration. Patients were assessed only based on ABI and no other modalities like Doppler or angiogram were used to evaluate the presence of PVOD. Depth of wounds, duration of diabetes, and presence of infected ulceration were not considered in the study.

CONCLUSION

The present study did not find any clinical or statistical difference in wound healing in the presence or absence of peripheral vascular occlusive disease. However, there was a remarkable reduction in wound surface area in both groups with time, after appropriate treatment with debriding agents and wound dressing. Patients with PVOD tend to have occlusion in both lower limbs and have a 40% chance of a compromised coronary arterial system which warrants early intervention, mandating extensive evaluation. Our study suggests the need to stratify patients with and without peripheral vascular disease and highlights the need to monitor wound healing over different time points in larger cohorts.

- Ethical considerations
- Acknowledgements
- Source of funding
- Conflicts of interest

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TABLES AND FIGURES

Table 1: Comparison of variables between groups

Variables	**Subcategory**	**Groups**		**Total**	***p*-value**
		With PVOD	**Without PVOD**		
Gender	Female	6 (30%)	6 (30%)	12 (30%)	1^{C}
	Male	14 (70%)	14 (70%)	28 (70%)	
Age (years)	<50	0	1 (5%)	1 (2.5%)	0.5212^{MC}
	50-59	3 (15%)	7 (35%)	10 (25%)	
	60-69	11 (55%)	8 (40%)	19 (47.5%)	
	70-79	5 (25%)	3 (15%)	8 (20%)	
	80-89	1 (5%)	1 (5%)	2 (5%)	
	Mean ± SD, Median (Min, Max)	65.6 ± 7.42, 64.5 (53, 84)	62.5 ± 9.5, 62 (49, 88)	64.05 ± 8.56, 63 (49, 88)	0.2572^{t}
ABI	Mean ± SD, Median (Min, Max)	0.67 ± 0.15, 0.7 (0.4, 0.8)	1.12 ± 0.17, 1.1 (0.9, 1.5)	0.9 ± 0.28, 0.9 (0.4, 1.5)	$< 0.001^{MW*}$
Hypertension	No	4 (20%)	9 (45%)	13 (32.5%)	0.0914^{C}
	Yes	16 (80%)	11 (55%)	27 (67.5%)	
Coronary artery disease	No	16 (80%)	17 (85%)	33 (82.5%)	1^{MC}
	Yes	4 (20%)	3 (15%)	7 (17.5%)	

Angioplasty	No	12 (60%)	20 (100%)	32 (80%)	0.0055MC*
	Yes	8 (40%)	0	8 (20%)	
Amputation	No	15 (75%)	18 (90%)	33 (82.5%)	0.4248MC
	Yes	5 (25%)	2 (10%)	7 (17.5%)	
Osteomyelitis	No	14 (70%)	14 (70%)	28 (70%)	1C
	Yes	6 (30%)	6 (30%)	12 (30%)	

*Abbreviation: ABI- Ankle brachial index, C – Chi square test, MC – Chi square test with Monte Carlo simulation, t – Two sample t test, MW – Mann Whitney U test, * indicates statistical significance at p<0.05.*

Figure 1: Distribution of gender over groups

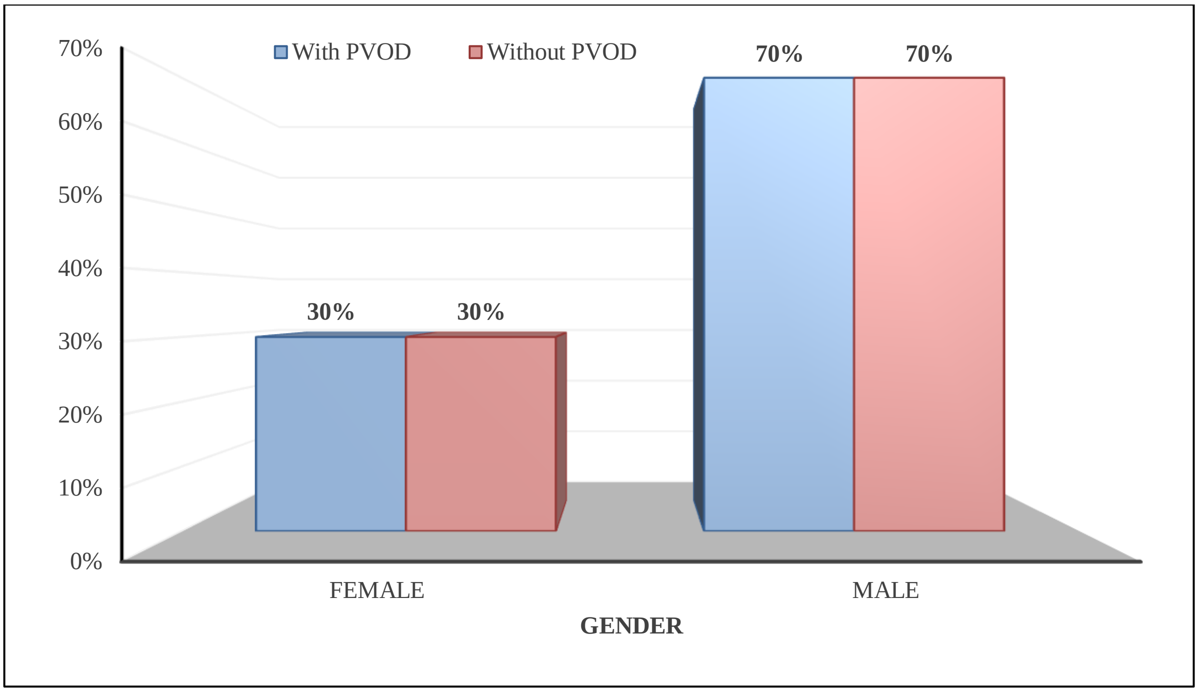

Figure 2: Distribution of age over groups

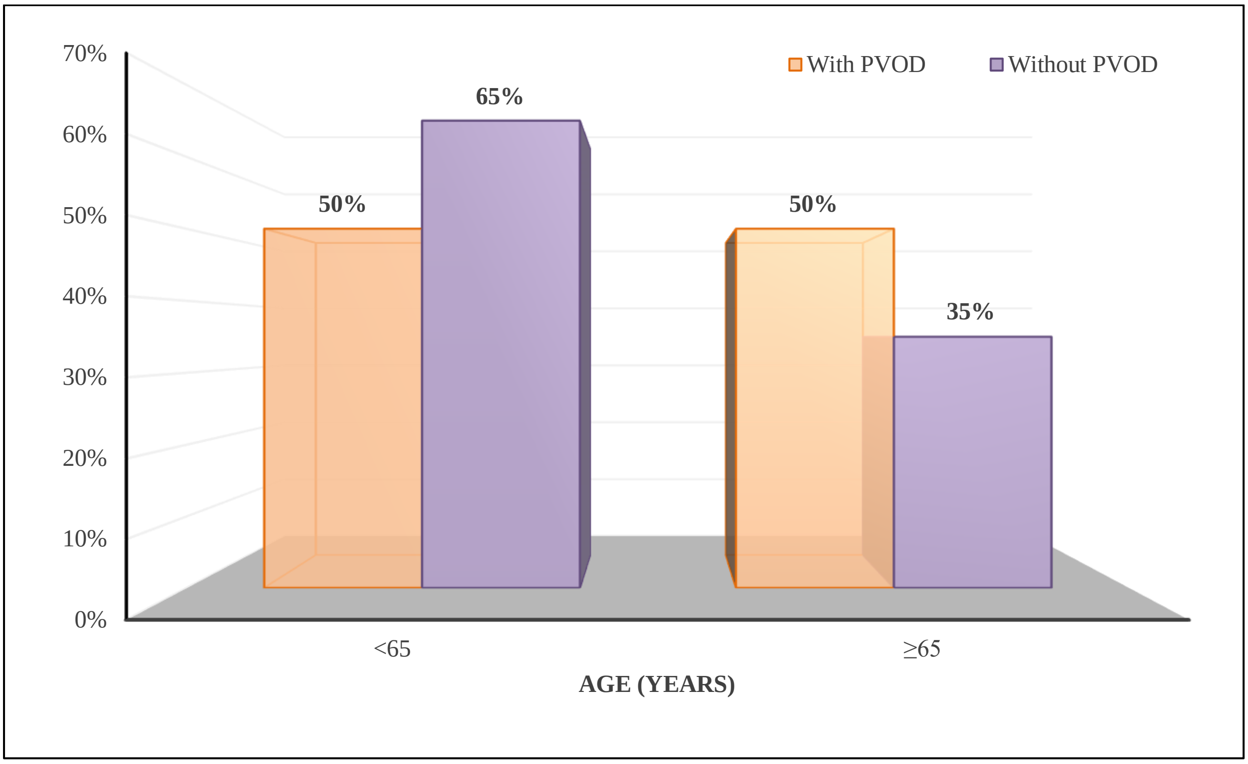

Figure 3: Distribution of CAD over groups

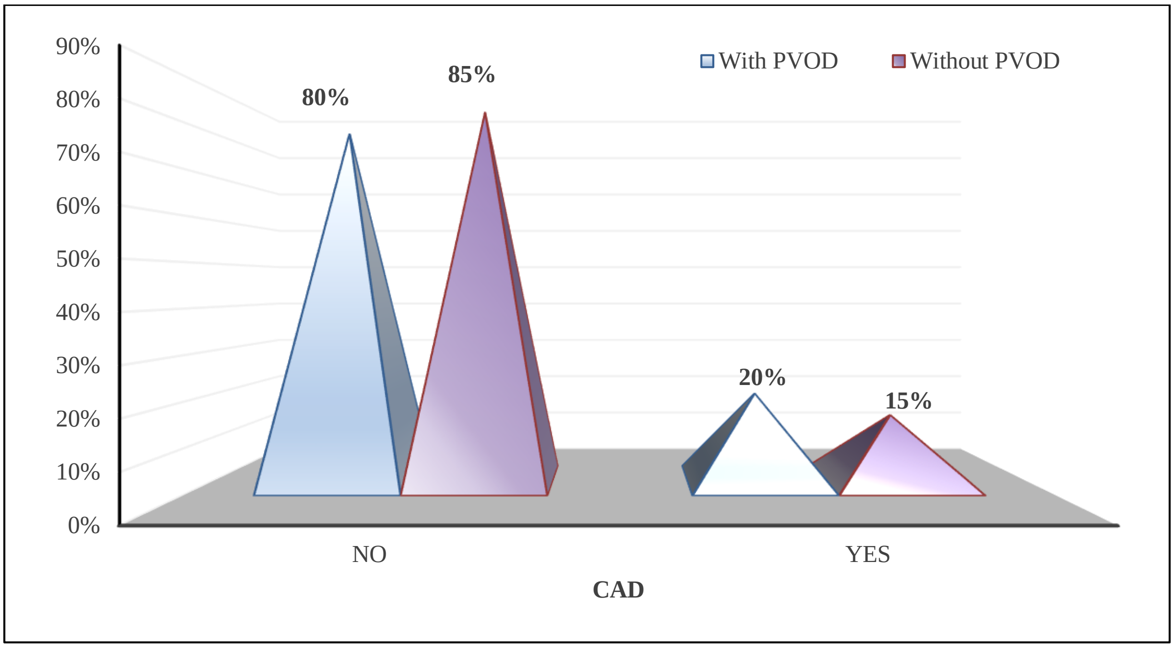

Figure 4: Mean plot of Surface area at different time points over group