

Efficacy of below-the-knee angioplasty for healing of therapy-refractory ischemic diabetic foot ulcers: A case-series study

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ABSTRACT

Background and Objectives: Diabetic patients are at high risk of therapy-refractory ischemic diabetic ulcers of the lower extremities. This study aimed to assess the efficacy of angioplasty for healing of therapy-refractory ischemic diabetic foot ulcers. **Materials and Methods:** This case series prospective study evaluated 40 hospitalized patients with therapy-refractory ischemic diabetic foot ulcers. Data regarding age, sex, hypertension, smoking status, end-stage renal disease (ESRD) and severity of ulcer before and after the intervention were collected using a researcher-designed questionnaire. Blood vessels with angiographic evidence of narrowing or arterial blockage underwent balloon angioplasty. Severity and healing of ulcers was scored using the Bates-Jensen criteria. Patients in whom, the severity of wound did not change after the surgical procedure were categorized as unhealed group while patients who experienced some degrees of healing were categorized as healed group. Data were analyzed using SPSS version 15 at $P < 0.05$ level of significance. **Results:** The ulcers healed in 80% of patients following the intervention. A significant difference was noted in the mean score of wound severity following angioplasty in the two groups of healed and unhealed patients ($P = 0.001$). The mean score of wound severity was compared before and after the intervention between healed and unhealed patients, males and females, subgroups with and without hypertension, subgroups with and without ESRD and smokers and non-smokers; the results showed that before the intervention, the mean score of wound severity was not significantly different in patients with/without the afore-mentioned risk factors ($P > 0.05$). After the intervention, however, the mean score of wound severity in patients with ESRD was significantly higher than that in patients without ESRD ($P = 0.003$). The results showed that healing did not depend on age, sex, presence/absence of hypertension or affliction with ESRD ($P > 0.05$). **Conclusion:** Angioplasty seems to be an efficient modality for healing of therapy-resistant ischemic diabetic foot ulcers. Further studies on larger sample size are required to assess the efficacy of this modality in patients with certain risk factors.

Keywords: Angioplasty, Diabetic foot ulcers, chronic wounds, therapy-refractory.

Introduction

Chronic, therapy-refractory ulcers are defined as wounds that

do not heal within one month following the initiation of treatment, and are considered a medical dilemma^[1]. Chronic, therapy-refractory ulcers have a high prevalence in different communities worldwide. A study conducted in Sweden reported the prevalence of therapy-refractory ulcers in the lower extremities to be one per 50 individuals^[2].

Therapy-refractory ulcers can be due to burns, diabetes mellitus, pressure sores, trauma, infections and inflammation^[1]. Evidence shows that diabetes mellitus is a predisposing factor for development of therapy-refractory ulcers in lower extremities, and diabetic patients are among the high risk groups in this respect. In 2012, 371 million people worldwide were suffering from diabetes mellitus; this rate is estimated to

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reach 552 million until 2030 [3]. It should be noted that about 80% of diabetic patients live in developing countries [4]. Annually, around one million diabetic patients lose part of their foot due to diabetic foot ulceration [5]. This preventable and treatable condition imposes high emotional and financial burden on patients and their family members and is also costly for the health care systems worldwide [6].

Pathophysiologically, ischemia and hypoxia play important roles in impaired healing of therapy-refractory ulcers. Both ischemia and hypoxia are related to arterial insufficiency, leading to cutaneous infections [7]. Peripheral artery disease in diabetic patients mainly occurs due to accelerated atherosclerosis and is considered an important risk factor for impaired wound healing and amputation of lower extremities [8]. Although ischemia is rarely the primary cause of development of foot ulcers, its presence negatively affects the healing of diabetic foot ulcer. The prognosis of such ulcers becomes worse if ischemia is accompanied by infection [9,10].

In general, management of peripheral artery disease includes medical, endovascular and surgical interventions. Medical treatment includes smoking cessation, weight loss and increased physical activity. Blood pressure medications, cholesterol lowering medications (statins) and anticoagulants may be prescribed as well [11]. Among endovascular and surgical interventions, percutaneous transluminal angioplasty (PTA) is commonly performed through the femoral artery. Patients who are not candidates for angioplasty may undergo open bypass surgery [12]. PTA has advantages over open surgery. For instance, it can be performed under local anesthesia and patients can resume their normal activity 24 to 48 hours, postoperatively. Also, angioplasty is repeatable [13].

Evidence shows that provision of adequate arterial blood supply to the ulcer is the first priority for wound healing and should be performed prior to any other procedure [14, 15]. In the recent years, researchers have focused on revascularization methods particularly angioplasty to provide sufficient blood supply aiming to enhance wound healing. However, number of prospective studies on the outcome of such techniques is limited. This study aimed to assess the efficacy of angioplasty for healing of therapy-refractory diabetic foot ulcers as an alternative to local treatments and supportive care.

Materials and Methods

This case-series prospective study evaluated 40 patients. Sample size was calculated to be 40 considering the wound healing rate of 67% by angioplasty [9], additional 10% of subjects to compensate for the possible dropouts, $d=0.15$ and $\alpha=0.05$. Forty hospitalized patients with diabetic foot ulcers in 2016 were included in this prospective study. All patients signed informed consent forms prior to participation in the study. Patients with therapy-refractory wounds suffering from coagulopathy, chronic liver disease, compromised immune system, coronary heart disease, autoimmune vasculitis, rheumatologic disorders and infected wounds associated with osteomyelitis were excluded.

A researcher-designed questionnaire was used for collection of data regarding age and sex of patients, hypertension, cigarette smoking, end-stage renal disease (ESRD) and severity of wound before and after the intervention.

All patients underwent a thorough clinical examination. The lower limb pulse was assessed and Doppler sonography was performed. Patients suspected for narrowing or blockage of the artery due to lack of lower limb pulse and according to Doppler sonographic findings, underwent peripheral vascular angiography. Vessels with angiographic evidence of narrowing or arterial blockage underwent balloon angioplasty.

Wound healing was evaluated by vascular surgeon in weekly visits. Healing and severity of wounds were scored according to the Bates-Jensen criteria [16], comprising of 15 items including shape, location, size, depth, edges, underlying tissue, necrotic tissue type, amount of necrotic tissue, granulation tissue, epithelialization, exudate type, exudate amount, surrounding skin color, edema and induration. A numerical score was not allocated to shape and location. Score 1 indicated complete wound healing while score 5 indicated most severe wound. Scores 13-20 indicated minimal, 21-30 indicated mild, 31-40 indicated moderate and 41 to 65 indicated extreme severity of wound.

Passage from one step to the next or going back to the previous step indicated healing or aggravation of wound, respectively.

In classification of wound healing, patients in whom, the severity of wound did not change after the surgical procedure comprised the unhealed group while those who experienced a reduction in severity of wound were classified as the healed group.

The mean and standard deviation (SD) values were reported for quantitative variables while frequency and percentage were reported for qualitative variables. The Kolmogorov-Smirnov test was applied to assess normal distribution of quantitative data. Parametric t-test was applied for comparison of groups in terms of normally distributed data. The mean severity of wound before and after the intervention was compared using paired sample t-test. Chi-square test and Fisher's exact test were applied for comparison of qualitative variables. Data were statistically analyzed using SPSS version 15 at $P<0.05$ level of significance.

Results

Forty patients that met the eligibility criteria were evaluated. There were no dropouts during the study period. The minimum age of patients was 51 years and maximum age was 81 years. Table 1 shows the mean and SD of age, sex and other risk factors evaluated in this study.

Table 1. Demographic information and characteristics of the risk factors in patients

	Number and frequency percentage	Mean± standard deviation
Males	34 (85%)	-
Females	6 (15%)	-

Presence of hypertension	33 (82.5%)	-
Absence of hypertension	7 (16.5%)	-
Presence of ESRD	12 (37.5%)	-
Absence of ESRD	38 (62.5%)	-
Smokers	9 (22.5%)	-
Non-smokers	31 (77.5%)	-
Mean age of male patients (yrs.)	-	66.15±1.59
Mean age of female patients (yrs.)	-	68.83±2.85
Overall mean age of patients (yrs.)	-	66.56±8.23

ESRD: End-stage renal disease

Next, the mean and SD of wound severity score in patients was compared before and after the intervention, between males and females, between patients with/without hypertension, with/without ESRD and smokers and non-smokers. The mean wound severity score was compared before and after the intervention separately for each risk factor. Table 2 summarizes the results in this respect.

Table 2. Comparison of the mean score of wound severity (paired t-test) in subgroups of patients with/without the risk factors (independent t-test) before and after PTA

Subgroups	Wound assessment score before PTA (mean± 2SD)	Comparison of wound assessment score between subgroups before the intervention	Wound assessment score after PTA (mean± 2SD)	Comparison of wound assessment score between subgroups after the intervention
1	Presence of hypertension	p=0.704	42.07 ±9.19	P=0.484
	Absence of hypertension		40.57 ±14.30	
2	Presence of ESRD	p=0.404	43.60 ±9.69	P=0.003
	Absence of ESRD		40.78 ±10.28	
3	Smokers	p=0.104	37.25 ±11.00	p=0.201
	Non-smokers		43.13 ±9.55	
4	Males	p=0.909	41.81 ±10.61	p=0.141
	Females		42.33 ±6.65	
Total			10.01 ±41.89	p=0.001

PTA: Percutaneous transluminal angioplasty; SD: Standard deviation; ESRD: End-stage renal disease

Next, wound healing in patients was evaluated taking into account the severity of wound and presence of risk factors. Of 40 patients, ulcers healed in 32 but did not heal in 8 patients. In other words, ulcers healed in 80% of patients after the intervention. The mean score of wound severity in patients was compared between the two groups of healed and unhealed patients, and in males and females, subgroups of patients with/without hypertension, with/without ESRD and smokers and non-smokers using appropriate statistical tests. The results are presented in Table 3.

Table 3. Comparison of the mean score of wound severity in healed and unhealed patients and in different subgroups using chi-square test and t-test

Variable	Healed	Unhealed	Result of comparison
Males	26 (65%)	8 (20%)	Fisher's exact test (P=0.318)
Females	6 (15%)	-	
Presence of hypertension	27 (67.5%)	6 (15%)	Fisher's exact test (P=0.611)
Absence of hypertension	5 (12.5%)	2 (5%)	
Presence of ESRD	11 (27.5%)	4 (10%)	Fisher's exact test (P=0.686)
Absence of ESRD	21 (52.5%)	4 (10%)	
Smokers	8 (20%)	1 (2.5%)	Fisher's exact test (P=0.655)
Non-smokers	24 (60%)	7 (17.5%)	
Total age (years)	66.10±9.20	68.38±7.40	independent sample t test: p=0.16
Wound assessment score before PTA	44.57±7.62	31.88±12.00	independent sample t test: p=0.02
Wound assessment score after PTA	17.67±4.89	22.63±11.81	independent sample t test: p=0.075

Discussion

Revascularization and enhancing the blood flow to the extremities is an efficient modality for healing of therapy-refractory chronic wounds. Previously published studies have emphasized the optimal efficacy of PTA for this purpose [17, 18]. Lower patient cost, availability and successful results are among the advantages of PTA [19, 20]. However, it also has shortcomings such as failure in healing of highly-calcified lesions or cases of chronic complete obstruction [21]. The results showed healing of 80% of cases in our study, and the mean severity of wound after the intervention was significantly lower in healed group compared to unhealed group (P=0.001). Muhs et al, in their study conducted in 2006 in the United States showed that revascularization method had a significantly higher success rate in wound healing compared to supportive treatments and in long-term, revascularization with angioplasty and stent placement, particularly medicated stents, improved the blood flow to the area by 95% and was associated with fast recovery and healing of ulcers [22]. Aust et al, in 2008 reported successful recanalization of artery and improved perfusion of wounds in all 34 cases evaluated in their study within a six-month period [23]. It should be noted that we did not have a control group and did not compare any other intervention with angioplasty in our study.

The difference in the mean score of wound severity in patients was compared between healed and unhealed groups, before and after the intervention, between males and females, in subgroups with and without hypertension, in smokers and non-smokers and in subgroups with and without ESRD. The results showed that before the intervention, the mean score of wound severity

was not significantly different between smokers and non-smokers, patients with and without hypertension and those with and without ESRD ($P>0.05$). But after the intervention, the mean score of wound severity in patients with ESRD was significantly higher than that in patients without ESRD ($P=0.003$). Also, the results showed that degree of healing did not depend on age, sex, hypertension or affliction with ESRD ($P>0.05$). This finding may be due to our small sample size in each of the subgroups, which decreases the reliability of the results, because evidence shows that cigarette smoking, ESRD, diabetes mellitus and heart failure play important roles in aggravation of chronic ulcers. Shailesh et al. evaluated the relationship of risk factors with severity of diabetic foot ulcers and found a significant association between the severity of wounds and tobacco use [24]. Pemayun et al, also pointed to a significant association between systolic and diastolic blood pressure and severity of wounds [25]. Thus, future studies with larger sample size are required on patients with certain risk factors to better elucidate this topic.

Conclusion

Considering the increasing use of angioplasty and its advantages including fewer complications, lower cost and shorter hospitalization period compared to supportive therapy, revascularization by angioplasty is recommended for patients with diabetic foot ulcers. Many patients can benefit from this treatment modality by its growing application in near future. Further studies with larger sample size are required on patients with certain risk factors to better elucidate this topic.

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