Comparison of the effects of cilostazol and aspirin on wound healing in patients with diabetic foot ulcer and peripheral artery disease

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Bayram Colak*, Atilla Orhan**, Ilhan Ece*, Serdar Yormaz*, Huseyin Yilmaz*, Mustafa Sahin*

**Department of General Surgery, Faculty of Medicine, Selcuk University, Konya, Turkey*
***Department of Cardiovascular Surgery, Faculty of Medicine, Selcuk University, Konya, Turkey**

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Diabetic foot ulcer (DFU) is one of the most feared complications of diabetes mellitus. Studies report that the lifetime-rate of developing DFU is 25% for patients with diabetes mellitus. In addition, peripheral artery disease (PAD) is seen in approximately 50% of patients with DFU. PAD increases the risk of amputation in patients with DFU and complicates treatment.
This study aimed to compare the effects of cilostazol and aspirin on wound healing in patients with DFU and PAD. In the study, DFU patients with PAD were retrospectively reviewed. They were divided into two groups. One group was administeredcilostazoland the other was administeredaspirin. Patients were evaluated according to their demographic characteristics, wound characteristics, PAD symptoms, duration of treatment, and treatment grades.
There were 30 patients in the cilostazol group and 20 patients in the aspirin group. Of the patients in the cilostazol group, seven(23.3%) had Wagner's grade 2, 16 (53.3%) had grade 3, and seven (23.3%) had grade 4 DFU. In the aspirin group this rate was 25%, 55%, and 20%, respectively. The mean size of the wound in the cilostazol group was 8.1 cm (2-25 cm), whereas it was 7.6 cm (5-25 cm) in the aspirin group. The mean ankle-brachial index (ABI) of the patients was 0.90 in the cilostazol group and 0.96 in the aspirin group. Five (23.3%) of the patients in the cilostazol group had triphasic, 19 (63.3%) biphasic, and six(20%) monophasic currents in the distal popliteal vein. In the aspirin group, these rates were 35%, 50%, and 20%, respectively. Of the patients in the cilostazol group, according to the Fontaine classification, six(20%) had stage 2A, 11 (36.7%) had stage 2B, 10 (33.3%) had stage 3, and three(10%) had stage 4 symptoms. In the aspirin group, these rates were 45%, 40%, 15%, and 0%, respectively. There was a complete response to treatment in 27 patients (90%) in the cilostazol group and 11 patients (55%) in the aspirin group. Partial response was present in the other patients. The mean duration of treatment was 1.31 months (1-2 months) in the cilostazol group and 1.82 months (1-2.5 months) in the aspirin group.
In this study, it was observed that wound healing was faster in the cilostazol group, complete response to treatment was higher, and improvement in PAD symptoms was better compared to the aspirin group.

KEY WORDS: Aspirin, Cilostazol, Diabetic foot ulcer

Introduction

Diabetic foot ulcer (DFU) is one of the most feared complications of diabetes mellitus. Studies report that the lifetime rate of developing DFU is 25% for patients with diabetes mellitus [1]. In addition, peripheral artery disease (PAD) is seen in approximately 50% of patients with DFU [2,3]. Studies have shown that PAD and infections are important factors affecting healing in patients with DFU [3]. When this study compared DFU patients with and without PAD, the rate of recovery in patients without PAD was 84%, whereas it was 69% in patients with PAD.
Studies recommend low doses of aspirin because of the high risk of cardiovascular disease in diabetic patients [4,5]. In patients with coronary stents, it has been reported

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Correspondence to: BayramColak, Department of General Surgery, Faculty of Medicine, Selcuk University, Konya Turkey (e-mail: bayro.99@gmail.com)

that patients with diabetes mellitus have an increased risk of thrombosis [6]. This is related to dysfunction in the platelets in diabetic patients [7]. Cilostazol, which has been used to reduce the risk of arterial thrombosis in all studies, has been reported to be more effective than aspirin [5,6].
This study aimed to compare the effects of cilostazol and aspirin on wound healing in patients with DFU and PAD.

Materials and Methods

The files of patients with DFU who had been treated and followed up in the General Surgery Clinic were retrospectively studied. Among these patients, those with PAD were divided into two groups: a cilostazol group and an aspirin group. Patients were evaluated according to their demographic characteristics, blood values, imaging examinations, duration of diabetes mellitus, wound characteristics, treatment method recovery status, and PAD conditions.
All patients were examined by endocrinology, cardiovascular surgery, radiology, and orthopedics before treatment.

Inclusion criteria
Patients over the age of 18 and under the age of 70 years (because advanced age can delay wound healing) were included in the study. Patients with Wagner's grade 1,2,3, and 4 and patients with DFU and PAD were included in the study.

Exclusion criteria
Wagner's grade 5 patients (because of the indications of amputation) and patients with major amputation needs [major amputation: transmetatarsal, tarsometatarsal (Lisfranc), intertarsal (Chopart), rear foot and foot-ankle amputations, and below knee amputations] were excluded from the study.Patients with cilostazol or aspirin allergy, patients with a history of cancer, immunosuppressed patients, non-diabetic patients with foot wounds due to vascular or dermatological reasons, patients with nephropathy, and patients without PAD were excluded from the study.

Patient groups
Group 1: cilostazol group
Group 2: aspirin group

Cilostazol and aspirin therapy
Cilostazol was administeredas 100 mg on a full stomach once a day.After having found that it didn't cause hypotension and headache (because these are the most common side effects of cilostazol), administration was increased to twice a day after about one week of treatment. Aspirinwas administrated as 100mg on a full stomach once a day. The treatment continued for approximately three months during hospitalization and after discharge.

Evaluation of infection and treatment
Infection symptoms were evaluated clinically. Purulent discharge at the base of the wound, hyperemia around the wound, abscess, temperature increase, induration, and infection symptoms were considered to be infected DFU. In addition, proliferation of microorganisms in culture was considered to be infected DFU. Cephalosporin group antibiotics were administered asbroad-spectrum antibiotics for all inpatients for 7-10 days. Antibiotic treatment was changed according to culture results. Antibiotic treatment for patients with osteomyelitis lasted for at least 14 days.

Evaluation of osteomyelitis
X Rays were used for diagnosis of osteomyelitis. Osteomyelitis was interpreted when cortical erosion and new periosteal bone formation was detected in the direct radiographs adjacent to ulcer and cellulitis. Magnetic resonance (MR) imaging was performedon these patients.

Evaluation of PAD diagnosis
Clinically, PAD was evaluated according to Fontaine classification [8];
Stage 1: Asymptomatic (PAD present and is not completely blocked)
Stage 2: Claudication pain; Stage 2A: Symptoms after more than 200 meters of free walking; Stage 2B: Symptoms in less than 200 meters of walking.
Stage 3: Rest pain
Stage 4: Foot necrosis or gangrene.

In these patients, failure to detect dorsalis pedis and tibialis posterior pulsations on physical examination, and no flow or biphasic flow seen with hand Doppler, were evaluated as PAD [4].
Detection of occlusion with Doppler ultrasound examination and monophasic flow in peripheral vessels were evaluated as PAD.
Ankle-brachial index (ABI) <0.95 was assessed as PAD [4]. The range of 0.95-1.30 was considered normal [4].
Failure to see flow and detection of obstruction in MR angiography was assessed as the presence of PAD.

Evaluation of the wound
Presence of infection, necrosis, ischemia and wound size were assessed by clinical examination.

Depth of wound was evaluated with Wagner-Meggit's classification.
Grade 1: Superficial ulcer.
Grade 2: Ulcer extension to ligament and muscles, without abscess or osteomyelitis.
Grade 3: Deep ulcer with cellulitis and abscess, and with osteomyelitis in general.
Grade 4: Ulcer with localized gangrene.
Grade 5: Extensive gangrenous involvement of the entire foot.
Wound healing was traced with planimetric methods (a transparent acetate was placed on the wound to draw the edges of the wound and to have information about the wound surface).

Evaluation of neuropathy
For the detection of diabetic peripheral neuropathy, monofilament and vibration tests were performed. Semmes-Weinstein 5.07/10 g was used for the monofilament test. It was applied to eight different zones in each sole. The test was considered positive if the patient did not feel anything, despite the application of the filament until it bent.

Medical treatment
Debridement was applied to patients with necrotic and infected DFU. Intralesional Epidermal Growth Factor (75 μg EGF, Heberprot-P®,HAS Biotech, Vitoria, Spain) was applied to patients without infected and necrotic DFU three times a week, intralesionally [10].

Evaluation of treatment
At least 75% coverage with granulation tissue on the wound, ability to cover the wound with graft or flap, and the entire wound covered with skin were considered successful treatment and complete recovery.
On the wound bed, less than 25% closure with granulation tissue was considered "no treatment response", 26-50% granulation tissue was considered "minimal response to treatment", 51-75% granulation tissue was considered "partial response to treatment", and more than 75% granulation tissue was considered "complete response to treatment" [10].

Termination of treatment
Complete response to treatment, necrosis progression, the need for major amputation, failure to continue regular treatment, and the development of complications related to treatment led to termination of the study for these patients.

Statistical Analyses
Data collection was performed using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and the evaluation of patient data was performed using Statistical Package for the Social Sciences version 20.0 program (SPSS, Inc., Chicago, IL, USA). For continuous variables, descriptive statistics were calculated and expressed as mean Standard deviation. Categorical variables were presented as numbers and percentages. Analysis of Chi-square test or Fisher's tests were used to compare the variables among groups. A p value of <0.05 was considered to be statistically significant.

Results

There were 70 patients with DFU and PAD. Twelve were excluded due to irregularly administered treatment, and eight were excluded due to missing records.

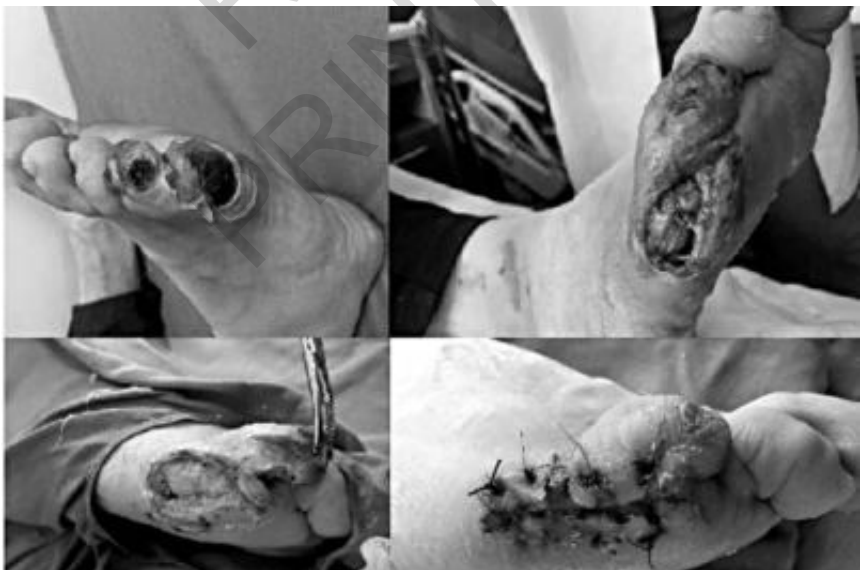

Fig. 1: Diabetic foot ulcer with infection and necrosis in cilostazol group. Only one phalanx amputation was performed instead of total finger amputation.

TABLE 1 - *Demographical and baseline characteristics and clinical outcome of the patients.*

Demographicaland clinical features	Cilostazol group (n. 30)	Aspirin group (n. 20)	p
Age (mean±SDyears)	56.5 ±10.1	54.8±9.2	0.65
Gender (%)			
Females	5 (16.6)	4 (20)	0.79
Males	25 (83.3)	16 (80)	0.64
Duration of diabetes (year)Median (25th 75th percentile)	18.4 (10-30)	16.8 (9-39)	0.55
Duration of diabeticfootulcer (month)	2.4 (1-8)	2.2 (1-7)	0.87
Neuropathy(%)	23 (76)	16 (78)	0.76
Infection (%)	22 (73.3)	12 (60)	0.40
Necrosis (%)	14 (46.6)	5 (25)	0.26
Wound size (cm) median (25th 75th percentile)	8.1 (2-25)	7.6 (5-25)	0.42
Woundlocalization (%)			
Footdorsal	1 (3.3)	1 (5)	0.26
Sole	7 (23.3)	4 (20)	0.84
Heel	3 (10)	2 (10)	1.00
Phalanges	9 (30)	7 (35)	0.78
Footlateral	2 (6.6)	1 (5)	0.94
Amputationstump (%)	8 (26.6)	5 (25)	0.89
Osteomiyelitis (%)	12 (40)	7 (35)	0.46
Number of intralesional EGF injections	12 (8-20)	21 (12-25)	<0.05
Meanduration of treatment (25th 75th percentile) (month)	1.31 (1-2)	1.82 (1-2.5)	<0.05
Wagner-Meggit'sclassification, n (%)			
Grade 1	0 (0)	0 (0)	
Grade 2	7 (23.3)	5 (25)	0.55
Grade 3	16 (53.3)	11 (55)	0.58
Grade 4	7 (23.3)	4 (20)	0.61
Outcome, n (%)			
Complete response (granulationtissue>75%)	17 (56.6)	8 (40)	<0.05
Partialresponse (granulationtissue 51-75%)	3 (10)	9 (45)	<0.05
No response	0 (0)	0 (0)	
Closingwithgraft (%)	6 (20)	11 (55)	<0.05
Complete closewith skin (%)	10 (33.3)	3 (15)	<0.05

P value was calculated by Student's t-test or Chi-square test. P<0.05 was considered statistically significant.

There were 30 patients in the cilostazol group. The mean age was 56.5 ± 10.1 years, with 16 (83.3%) males and five (16.6%) females. There were 20 patients in the aspirin group. The mean age was 54.8 ± 9.2 years, with 16 (80.0%) males and four (20.0%) females. The demographic and clinical findings of the patients are presented in Table I. In the cilostazol group, 16 (53.3%) patients had hypertension (HT) and two (6.6%) had chronic obstructive pulmonary disease (COPD). In the aspirin group, eight (40.0%) patients had HT and two (10.0%) had COPD. In the cilostazol group, 24 patients (80%) were treated with insulin, while this rate was 15 (75%) in the aspirin group. The mean duration of diabetic disease was 18.4 years (1-30 years) in the cilostazol group and 16.8 years (9-29 years) in the aspirin group. The duration of DFU diagnosis was 2.4 months (1-8 months) in the cilostazol group and 2.2 months (1-7 months) in the aspirin group. Eight patients (26.6%) in the cilostazol group had previously undergone amputation, while five (25%) in the aspirin group had undergone amputation. Of the patients in the cilostazol group, seven (23.3%) had Wagner's grade 2, 16 (53.3%) had grade 3, and seven (23.3%) had grade 4 DFU. In the aspirin group, this rate was 25%, 55%, and 20%, respectively. In the cilostazol group, 22 patients (73.3%) had infection, 14 (46.6%) patients had necrosis (Fig. 1), and threehad fasciitis. Revascularization was performed in threeof these patients by interventional radiology. In the aspirin group, 12 (60.0%) patients had infection. Necrosis was present in five (25.0%) of these patients (Fig. 2), and two had fasciitis. In the cilostazol group, DFU was present in the fingers of nine patients (30.0%), in the soles of seven (23.3%), in the heel ofthree (10.0%), in the lateral foot of two (6.7%), in the dorsal foot of one (3.3%), and in the amputation site of eight (26.7%). In the aspirin group, DFU was present in the fingers of seven patients (35.0%), in the soles in four (20.0%), in the lateral foot of one (5.0%), in the dorsal foot of one (5.0%), and in the amputation site in five (25.0%). The mean size of the wound in the cilostazol group was 8.1 cm (2-25 cm), whereas it was 7.6 cm (5-25 cm) in the aspirin group. In the cilostazol group, 12 (40.0%) patients had osteomyelitis. In the aspirin group, seven(35.0%) patients had osteomyelitis. The mean ABI index of the patients was 0.90 in the cilostazol group and 0.96 in the aspi-

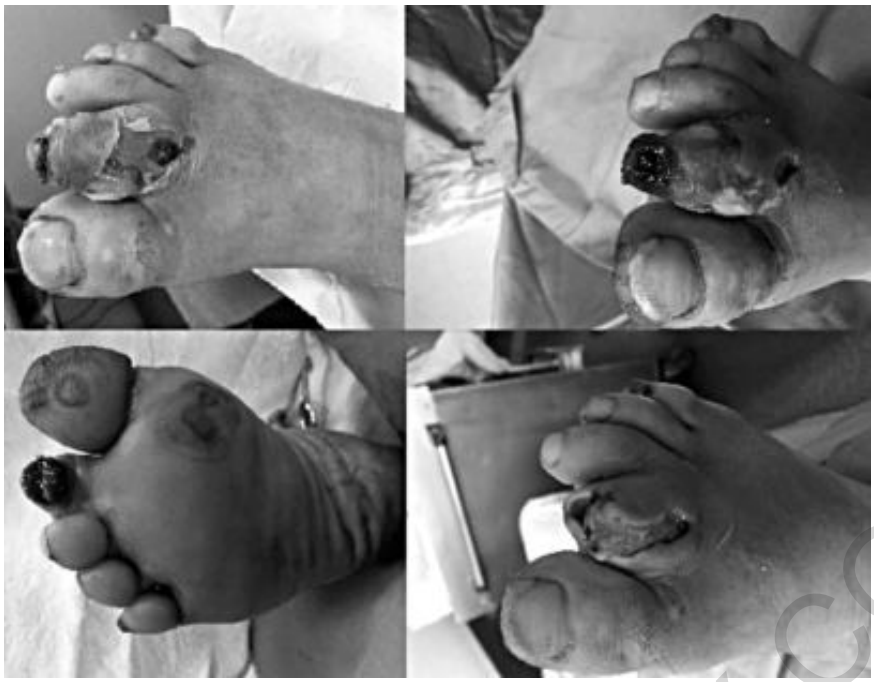

Fig. 2: Diabetic foot ulcer with infection and necrosis in aspirin group. Treated with medical treatment without amputation.

Table II - *Peripheral arterial findings of patients*

Peripheral artery disease findings of patients	**Cilostazol group (n. 30)**	**Aspirin group (n. 20)**	**p**
Fontaine classification, n (%)			
Stage 1	0 (0)	0 (0)	
Stage 2A	6 (20)	9 (45)	0.26
Stage 2B	11 (36.6)	8 (40)	0.85
Stage 3	10 (33.3)	3 (15)	0.24
Stage 4	3 (10)	0 (0)	0.06
Doppler USG, n (%)			
monofazik	6 (20)	4 (20)	0.15
bifazik	19 (63.3)	10 (50)	0.66
trifazik	5 (23.3)	6 (35)	0.52
ABI, n (%)			
<0.95	22 (73.3)	13 (65)	0.34
0.95-1.30	6 (20)	7 (35)	0.48
>1.30	2 (6.6)	0 (0)	0.07

P value was calculated by Student's t-test or Chi-square test. P<0.05 was considered statistically significant.

rin group. Five (23.3%) of the patients in the cilostazol group had triphasic, 19 (63.3%) biphasic, and 6 (20%) monophasic currents in the distal popliteal vein. In the aspirin group, these rates were 35%, 50%, and 20%, respectively. There was a complete response to treatment in 27 patients (90%) in the cilostazol group and in 11 patients (55%) in the aspirin group (p<0.05). Partial response was present in the other patients. The mean duration of treatment was 1.31 months (1-2 months) in the cilostazol group and 1.82 months (1-2.5 months) in the aspirin group (p<0,05).

Of the patients in the cilostazol group, six (20%) had stage 2A, 11 (36.6%) had stage 2B, 10 (33.3%) had stage 3, and three (10%) had stage 4 symptoms, according to the Fontaine classification. The rate of peripheral neuropathy in the cilostazol group was 76% (23 patients). After cilostazol therapy, there was an improvement of 86% in the leg symptoms of the patients (Table II).

Of the patients in the aspirin group, nine (45%) had stage 2A, eight (40%) had stage 2B, and three(15%) had stage 3 symptoms, according to the Fontaine classification (Table 2). The peripheral neuropathy rate in the aspirin group was 78% (16 patients). After aspirin therapy, there was a 65% improvement in the leg symptoms of the patients.

Discussion

In the study, patients with DFU were evaluated for PAD. Cilostazol and aspirin were used as antiaggregant treat-

ment to compare their effects on wound healing. Aninadequate number of articles comparing the effects of cilostazol and aspirin on wound healing was found in the literature. Despite the positive aspects of this study, its retrospective nature and limited number of patients are among its limitations.

Peripheral polyneuropathy, PAD, infection, and other comorbidities are also present in patients with DFU (3). Almost all DFU patients have diabetic neuropathy, and in the vast majority of them, neuropathy is accompanied by ischemia [8]. Peripheral neuropathy was present 76% in cilostazol group and 78% of patients in aspirin group in our study.

PAD is usually seen in the lower extremities and the first complaint is pain presenting as claudication [8]. In its later stages, pain that is relieved at rest is replaced by aches that persist even at rest [8]. In this study, all of the patients had stage 2A, 2B, 3, and 4 symptoms, according to the Fontaine classification. After treatment, there was an 86% improvement in the cilostazol group and a 65% improvement in the aspirin group in the patients' leg symptoms.

Claudication, resting pain, undetected foot pulse, monophasic flow in the Doppler, and ABI<0.9 are among the methods used for diagnosis of PAD [4,11]. These methods were used to diagnose PAD in patients with DFU in this study. ABI below 0.9 is important for the diagnosis of PAD. In this study, patients with ABI less than 0.9 were considered to have PAD. In some patients, ABI values can be greater than 1.3, depending on calcification in the peripheral arteries [12]. Although it is not an accurate indicator of vascular occlusion, it is important for diabetic patients due to high cardiac risk [12,13]. In two patients in the cilostazol group, ABI>1.3 was found.

Wagner's Megitt classification was used to evaluate the wounds of DFU patients. There are many classifications of DFU. The University of Texas classification evaluates the wound according to the depth of the wound and the presence of infection and ischemia, but does not include the ulcer site [14]. The SAD classification system classifies ulcers according to size, area, depth, sepsis, arteriopathy, and denervation [15]. The PEDIS classification system classifies wounds based on perfusion, surface area, depth, infection, and sensation [16]. The American Infectious Diseases Council has classified diabetic foot injuries as mild, moderate, and severe [17]. It is easy to understand and apply theWagner's Meritt classification system in this study, which classifies DFU according to the depth of the wound and the extent of the gangrene [14].

In our study clinic, an antiaggregant or antithrombotic therapy, such as aspirin or cilostazol, is started during and after wound treatment in patients with DFU. This is because studies have shown that diabetes mellitus is a high-risk trigger for PAD and causes high mortality and amputations [18]. PAD atherosclerosis causes diabetic foot lesions. It is known that atherosclerosis begins earlier and progresses more rapidly and aggressively in diabetic patients than in other patients [8], and that DFU patients with PAD have a lower chance of recovery with treatment [4]. For this reason, treatment of PAD also plays an important role in the treatment of DFU, as well as infection treatment.

In diabetic patients, peripheral vascular events are usually manifested by blockages that involve long segments in the leg veins [19,20]. Medial sclerosis characterized by calcification of the tunica media greatly reduces the flexibility of peripheral vessels and tissue perfusion [4]. A number of microvascular abnormalities have been reported in diabetic patients, such as arteriovenous shunting and deterioration of vascular activity [21]. These adverse changes result in capillary hypoperfusion and deterioration in wound healing in patients with diabetes mellitus [22]. In addition, an increase in cardiovascular risks has been reported due to functional disorders in the platelets of diabetic patients [7,23]. One study has reported that platelet surface flow had been decreased in diabetic patients compared to non-diabetic patients, and that the number of platelet microparticles in circulation had been increased [24]. Therefore, in order to fight against DFU, it is necessary to fight PAD at the same time.

Aspirin and cilostazol in the treatment of PAD have been compared in various publications [25-27]. Aspirin, which irreversibly inhibits the activity of the COX-1 enzyme in platelets, is recommended by the American Diabetes Association (ADA) to reduce the risk of cardiovascular disease in patients with diabetes mellitus (28). Cilostazol is a selective inhibitor of phosphodiesterase 3, which increases intracellular cAMP and active protein kinase [29]. Thus, cilostazol both inhibits platelet aggregation and performs vasodilatation (29). In studies comparing aspirin and cilostazol in diabetic and non-diabetic patients, cilostazol has been reported to be more effective than aspirin [25-27]. However, in the literature review, no studies comparing aspirin and cilostazol in wound treatment in diabetic patients were found. Because of the risk of PAD in diabetic patients, aspirin or cilostazol are administered in the treatment of all diabetic patients in our clinic. In this study, the rate of wound healing, the rate of complete closure with granulation tissue, and the rate of complete closure with skin were higher in the cilostazol group patients than in the aspirin group patients.It was also found that patients in the cilostazol group had faster and higher recovery rates in their leg symptoms.

Conclusion

Due to the risk of PAD in patients with DFU, it is necessary to start an antiaggregant treatment such as aspirin or cilostazol. As a result of this study, it can be said that the use of cilostazol is more effective than aspiri-

nin the improvement of symptoms of PAD, leading to a more comfortable lifestyle and effective treatment of DFU. Cilostazol is more effective in wound healing in DFU patients than aspirin. However, randomized and controlled studies are needed as further research.

Riassunto

Le ulcere del piede diabetico (DFU) è una delle complicazioni più temute del diabete mellito. Gli studi riportano che il tasso di incidenza dell'ulcera diabetica del piede (DFU) è del 25% per i pazienti con diabete mellito per tutta la loro vita. Inoltre, la malattia delle arterie periferiche (PAD) è presente in circa il 50% dei pazienti con DFU ed aumenta il rischio di amputazione nei pazienti con ulcera diabetica del piede e complica il relativo trattamento.
Questo studio mira a confrontare gli effetti di Cilostazolo e Aspirina sulla guarigione delle ferite in pazienti con ulcera diabetica del piede e PAD.
Materiale e metodi: nello studio, i pazienti con ulcera del piede diabetico con PAD sono stati esaminati retrospettivamente. Sono stati suddivisi in gruppo trattato con Cilostazolo e gruppo trattato con Aspirina. I pazienti sono stati valutati in base alle loro caratteristiche demografiche, caratteristiche della ferita, sintomi PAD, durata del trattamento e gradi di trattamento.
Dai risultati risulta che c'è stata una risposta completa al trattamento in 27 pazienti (90%) nel gruppo Cilostazol e in 11 pazienti (55%) nel gruppo Aspirina. La risposta parziale era presente in altri pazienti. La durata media del trattamento è stata di 1,31 mesi (1-2 mesi) nel gruppo Cilostazol e di 1,82 mesi (1-2,5 mesi) nel gruppo Aspirina.
Conclusioni: in questo studio, è stato osservato che la guarigione della ferita era più rapida nel gruppo Cilostazolo, la risposta completa al trattamento era più alta e il miglioramento dei sintomi della PAD era migliore rispetto al gruppo Aspirina.

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