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Influence of Peripheral Arterial Disease on Wound Healing in Heel Pressure Ulcers

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Background: There are cases of heel pressure ulcer with peripheral arterial disease (PAD). The influence of ischemia on wound healing was investigated.

Methods: We retrospectively studied 253 patients with heel ulcers treated between January 2003 and March 2018. The patients were classified into PAD and non-PAD groups. The wound healing rate, wound healing time and the factors that influenced wound healing were examined.

Results: There were 186 patients with PAD (73.5%). There were 41 (22.0%) and 35 (52.2%) wound healing cases with PAD and non-PAD, respectively (P < 0.001). In the non-PAD group, the deeper the ulcer, the lower the wound healing rate. However, in the PAD group, the increase in blood flow owing to revascularization affected the wound healing rate. The wound healing rate in the endovascular therapy (EVT) and bypass groups were 26.7% and 65.0%, respectively (P = 0.003). The wound healing time was 128 (interquartile range [IQR] 88－196) and 79 (IQR 35.5－187) days, with PAD and non-PAD, respectively (P = 0.0268). The wound healing time in the PAD group was 128 (IQR 93－174.5) days with bypass and 155.5 (IQR 86－237.5) days with EVT (P = 0.459).

Conclusions: Heel pressure ulcers with PAD are difficult to treat. The wound healing rate was lower in the PAD than in the non-PAD group and the wound healing time also tended to be long. Successful revascularization is important for wound healing and bypass surgery had a shorter wound healing time and a higher wound healing rate than EVT.

INTRODUCTION

Pressure ulcers are caused by friction and slippage. The heel is a common site for pressure ulcers, and some patients diagnosed with pressure ulcers have peripheral arterial disease (PAD). The relationship between heel pressure ulcer and PAD has been described before (1-3). Heel pressure ulcers with PAD are considered to reduce wound healing. We retrospectively investigated the cases of heel ulcers that were diagnosed at our hospital; the influence of ischemia on wound healing was also investigated.

Amputation-free survival (AFS), a composite endpoint of mortality and amputation, is commonly used as an indicator of the effectiveness of revascularization of the lower extremities. AFS is not equal to the wound healing rate, since even if the wound is not healed, the AFS will be high if the patients are alive. Healing the wound is not the only goal of treatment. Decline in activities of daily living and a worsening of prognosis should be considered before wound healing. However, we plastic surgeons need to predict the time to restoration of the wound condition and plan a comprehensive treatment. We investigated the wound healing rate, wound healing time and the factors influencing wound healing. Further, we examined the difference in the wound healing rate based on the revascularization method in the PAD cases.

MATERIALS AND METHODS

We included 253 patients with heel ulcers who were treated at the Department of Surgery & Wound Treatment Center in Shin-Suma General Hospital from January 2003 to March 2018. We included patients with heel ulcers, which were considered pressure ulcers, paraplegia due to spinal cord injury, or hemiplegia owing to cerebrovascular accident, and patients who were bedridden. Patients with PAD who developed a new heel ulcer

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during follow-up for other foot ulcers were also included. Heel ulcers due to acute trauma, such as burns and bone fractures, were excluded.

In cases where the dorsal and posterior tibial arteries were difficult to palpate, blood flow was determined using the Doppler ultrasonic stethoscope. The diagnosis of PAD was made when the skin perfusion pressure (SPP) was 40 mmHg or less (4,5), and computed tomographic angiography, magnetic resonance angiography, and angiography revealed stenosis or occlusion of the lower limb artery.

The depth of the ulcer was determined using the pressure ulcer staging of the National Pressure Ulcer Advisory Panel (Figure 1) (6). Cases with only redness (Stage I) were excluded. Stage III and IV were defined as deep ulcers.

Patients with heel ulcers were divided into two groups: the PAD and non-PAD groups. We investigated the age, sex, comorbidities (diabetes mellitus [DM], hemodialysis [HD], spinal cord injury, cerebrovascular disease and dementia), wound condition (size and depth of the ulcer), and outcome. The influence of the depth of the ulcer on wound healing and wound healing time was subsequently compared. The wound healing time was defined as the period from the start of treatment at our hospital to the healing of the wound. Flowchart of the treatment of the heel ulcer at our hospital is shown (Figure 2). Treatment was performed according to this flowchart. Treatments (diabetes control, nutritional status improvement, antibiotic administration, off-loading, debridement, negative pressure wound therapy [NPWT] or skin grafting) except revascularization were performed similarly in both the PAD and non-PAD groups.

In addition, we investigated the method of revascularization and the factors that influence wound healing, in the PAD group. The cases of revascularization for PAD were classified into endovascular therapy (EVT) or bypass groups. The decision to perform EVT or bypass was based on the general condition, condition of the blood vessels, wound size and depth of the ulcer. Those in whom both EVT and bypass were performed were included in the bypass group.

Statistical analysis

Normally distributed continuous data were expressed as mean ± standard deviation, and compared using the Welch's t-test, whereas non-normally distributed data were expressed as median and interquartile range (IQR) and compared using the Mann–Whitney’s U-test. Categorical data were expressed as numbers and percentages and compared using the Fisher's exact test. P values <0.05 were considered statistically significant.

(A) (B) (C)

Figure 1. The staging of the heel ulcer depth

(A) Stage II: A partial thickness skin loss involving the epidermis or dermis or both.
(B) Stage III: A full thickness skin loss without exposed bone, tendon or muscle.
(C) Stage IV: A full thickness skin loss with exposed bone, tendon or muscle.

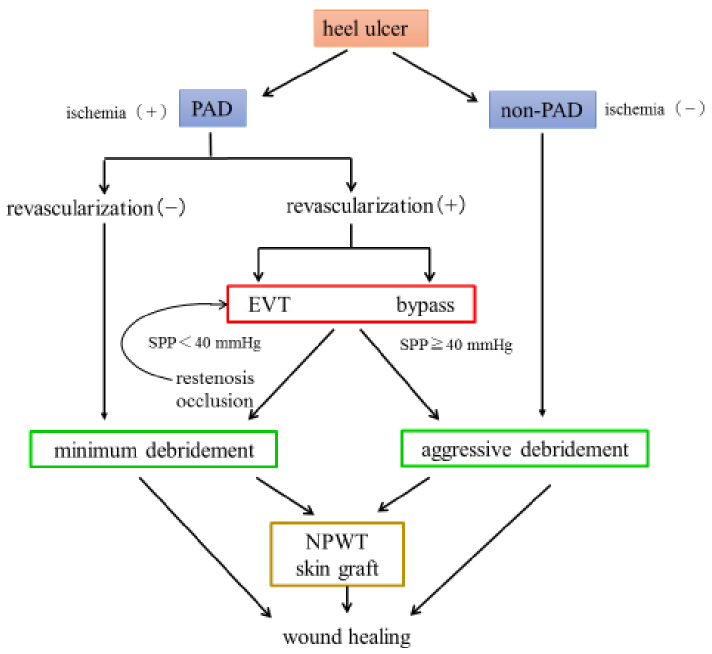

Figure 2. Flowchart of the treatment for heel ulcers
First, examine the blood flow in the lower extremities to check if a patient with heel ulcer has PAD. Aggressive debridement with SPP of 40 mmHg or less owing to lower limb ischemia causes increased necrosis. Therefore, if lower limb ischemia is present, revascularization should be performed first. After successful revascularization, aggressive debridement should be performed. In addition, when vascular stenosis or occlusion occurred during treatment, revascularization treatment should be repeated again. In cases in which revascularization could not be performed, minimum debridement should be performed.

RESULTS

Among the 253 patients with heel ulcers, there were 186 patients with PAD (73.5%). The clinical characteristics of all the patients in both the PAD and non-PAD groups are shown in Table I. Most of the patients with DM and HD were in the PAD group while most of the patients with spinal cord injury were in the non-PAD group. There was no significant difference in cerebrovascular disease and dementia between the PAD and non-PAD groups. Although there was variability in the ulcer size, it was not significantly different between the PAD and non-PAD groups. However, there were more deep ulcers in the PAD group ($P < 0.001$).

The outcomes of the 253 patients with heel ulcers are shown in Table II. Seventy-six patients had healed wounds (30.0%). There were 41 (22.0%) and 35 (52.2%) wound healing cases with PAD and non-PAD, respectively. The rate of the wound healing was significantly lower in the PAD group than in the non-PAD group ($P < 0.001$). The wound healing time was 128 (IQR 88-196) and 79 (IQR 35.5-187) days, in the PAD and non-PAD groups, respectively. The wound healing time was longer in the PAD group than in the non-PAD group ($P = 0.0268$). Thirty-one patients died during the treatment (30 cases of PAD, 1 case of non-PAD). Two patients with PAD died from sepsis and necrosis of the foot ulcers. The causes of death in the other 29 patients were ischemic heart disease, heart failure, cerebral ischemia, gastrointestinal bleeding, and pneumonia. During treatment of the heel ulcers, patients with PAD had a higher probability of dying from comorbidities than those without PAD ($P < 0.001$). In addition, there were 12 cases of lower extremity amputation (11 cases with PAD, 1 case of non-PAD) ($P = 0.192$).

Regarding the depth of the ulcer, in the non-PAD group, the shallower the ulcer, the higher the wound healing rate. Meanwhile, in the PAD group, there was no significant difference in the wound healing rate between stage III and stage IV ulcers (Table III). In the non-PAD group, the depth of the ulcer affected the wound healing rate; however, in the PAD group, which had many cases with deep ulcers, the influence of depth on wound healing was low.

Table I. The characteristics of the 253 patients with heel ulcers

	PAD cases n = 186	non-PAD cases n = 67	P value
Age (years)	74.7 ± 9.6	74.5 ± 17.6	0.921
Sex (male)	114 (61.3%)	32 (47.8%)	0.06
Comorbidities			
Diabetes mellitus	127 (68.3%)	27 (40.3%)	<0.001
Hemodialysis	91 (48.9%)	5 (7.5%)	<0.001
Spinal cord injury	1 (0.5%)	7 (10.4%)	<0.001
Cerebrovascular disease	36 (19.4%)	11 (16.4%)	0.715
Dementia	21 (11.3%)	13 (19.4%)	0.0995
Wound condition			
Size (cm^2)	3.6 (1.3－8.3)	3.3 (1.3－6.9)	0.764
Deep ulcer	181 (97.3%)	51 (76.1%)	<0.001

Table II. The outcome of the 253 patients with heel ulcers

	PAD cases n = 186	non-PAD cases n = 67	P value
Heal wounds	41 (22.0%)	35 (52.2%)	<0.001
Healing time (days)	128 (88－196)	79 (35.5－187)	0.0268
Death	30 (16.1%)	1 (1.5%)	<0.001
Major amputation	11 (5.9%)	1 (1.5%)	0.192

Table III. Wound healing cases and wound healing rates for each ulcer stages

	PAD	non-PAD
Stage II	3/5 (60.0%)	12/16 (75.0%)
Stage III	22/112 (19.6%)	18/39 (46.2%)
Stage IV	16/69 (23.2%)	5/12 (41.7%)

We investigated the factors that influence the wound healing rate in the PAD group (Table IV). There were no significant differences in the comorbidities or wound condition between the healed cases and non-healed cases. Hemodialysis is considered a factor in the reduction and delay of wound healing (7,8). However, at our facility, the influence of dialysis on wound healing rate was low. Only revascularization affected the wound healing rates ($P < 0.001$). Revascularization was performed in only 80 cases (43.0%) with PAD. Revascularization was not performed in the other cases with PAD because the patients were unable to lie down owing to dementia, or extend the lower limbs owing to joint contracture, and were in poor general condition. In addition, revascularization was not performed in those who did not have blood vessels through which the catheter could pass or could be connected by bypass. Furthermore, there were cases in which revascularization treatment was not desired.

Table IV. Analysis of the factors affecting wound healing in the PAD group

	Healed cases n = 41	non-healed cases n = 145	P value
Age (years)	73.0 ± 9.1	75.2 ± 9.7	0.171
Comorbidities			
Diabetes mellitus	26 (63.4%)	101 (69.7%)	0.453
Hemodialysis	18 (43.9%)	73 (50.3%)	0.485
Wound condition			
Size (cm^2)	3.2 (1.4－7.0)	3.8 (1.3－8.3)	0.789
Deep ulcer	38 (92.7%)	143 (98.6%)	0.0721
Revascularization	29 (70.7%)	51 (35.2%)	<0.001

Among the 80 revascularization cases, 60 were EVT and 20 were bypass (Table V). There were many cases of EVT (75.0%). The wound healing rate in the EVT and bypass groups were 26.7% and 65.0%, respectively. The wound healing rate was higher with bypass than EVT (P = 0.003). Of the 16 cases healed in EVT, 4 underwent repeated revascularization owing to restenosis or vascular occlusion during the treatment time (Table VI). On the other hand, bypass graft occlusion occurred in only one of the 13 healed cases and underwent additional EVT once for that graft occlusion. EVT required an average of 1.44 (up to 4) times revascularizations to heal the wound. Although there was no significant difference, EVT had a higher vascular stenosis and occlusion rate than bypass, and in many cases, repeated revascularization was required before wound healing. Angiosome represents the anatomical blood circulation area of the main blood vessels. The foot is supplied by the three major arteries (anterior tibial artery, posterior tibial artery and peroneal artery); between the arteries, there are numerous arterial-arterial connections (9,10). Revascularization of blood vessels that directly feed the wound based on the angiosome concept reportedly has a higher limb salvage rate than indirect revascularization (10). The heel is supplied by the calcaneal branch of the peroneal and posterior tibial arteries. Therefore, we mainly performed revascularization for the posterior tibial artery and the peroneal artery. However, in cases where both of them were occluded, we performed indirect revascularization for the anterior tibial artery and the dorsalis pedis artery since blood flow could be supplemented through the arterial-arterial connection. In the arterial region below the knee, of the 7 healed wound cases, only 1 underwent EVT of the anterior tibial artery. In the bypass group, dorsalis pedal artery bypass was performed in 4 out of the 7 healed wound cases.

Table V. PAD cases undergoing revascularization

	EVT n = 60	bypass n = 20	P value
Wound healing	16 (26.7%)	13 (65.0%)	0.003

Table VI. PAD cases with wound healing following revascularization

	EVT n = 16	bypass n = 13	P value
Occlusion	4 (25.0%)	1 (7.7%)	0.343
Revascularization (times)	1.44 (1－4)	1.08 (1－2)	0.217

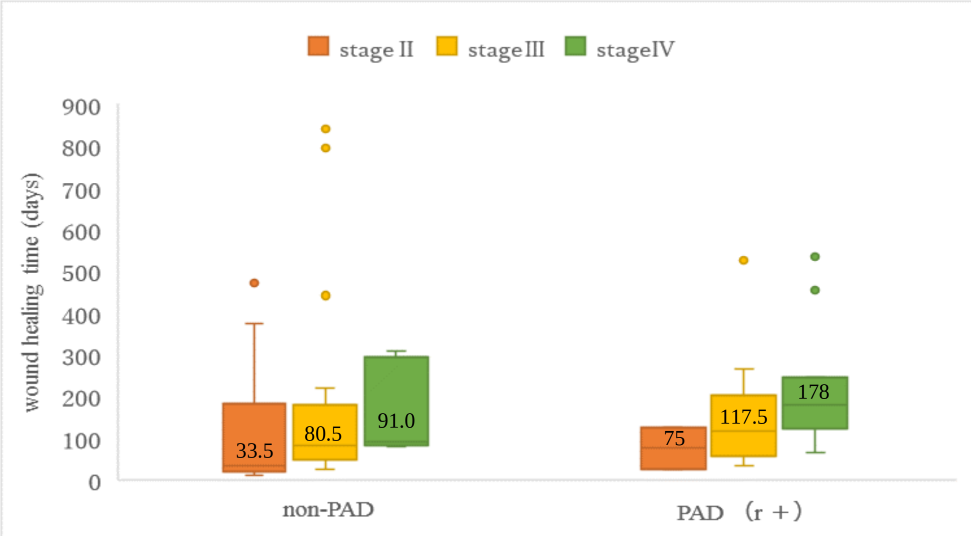

Figure 3. Wound healing time for each stage of the heel ulcer between non-PAD and PAD (r＋) cases

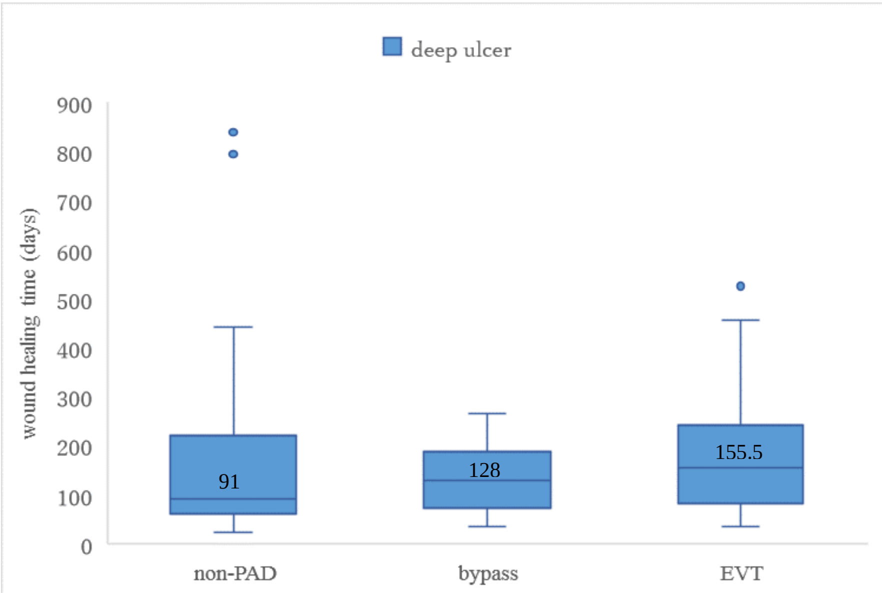

Figure 4. Wound healing time for deep ulcers between non-PAD and PAD (r＋) cases

Although the wounds healed without revascularization in a few cases in the PAD group, revascularization is important for wound healing for the PAD group. The wound healing time for each stage of the ulcer was compared between the non-PAD group and the revascularized PAD (PAD (r +)) group (Figure 3). The non-PAD group showed variability in the wound healing time; however, in both the PAD (r +) and non-PAD groups, the deeper the ulcer, the longer the wound healing time tended to be. The wound healing time of a deep ulcer requiring more medical intervention to treat in the PAD (r +) and the non-PAD group were 133 (IQR 80－212) and 91 (IQR 61－220) days, respectively (P = 0.189). Although there was no significant difference, the PAD (r +) group, tended to take longer to heal the wound than the non-PAD group. In the PAD (r +) group, healing in the bypass group was 128 (IQR 93－174.5) days and the EVT group was 155.5 (IQR 86－237.5) days (P = 0.459) (Figure 4). Although there was no significant difference, EVT cases tended to take longer to heal the wound than bypass cases.

DISCUSSION

Whether heel ulcers are due to pressure ulcers or are symptoms of PAD is often debated (2). The overall wound healing rate of heel ulcer was 30.0%, and the wound healing rate was only half even in the non-PAD group. Moreover, the wound healing rate was further reduced in patients with PAD. The reason was that many patients with heel ulcers were elderly. In many cases, the treatment was not completed because of the patients being transferred to another hospital during treatment, poor general condition, or worsening of other diseases. In particular, many PAD cases were complicated by DM and HD, and many patients died from comorbidities other than the foot ulcer during treatment. In addition, pressure ulcers frequently occur on the heel than other locations on the foot (toe, forefoot and midfoot), which could explain the decrease in the rate of wound healing. Several studies have compared the difference in the wound healing rate based on the wound location on the foot in cases with PAD (7,11-13). The healing rate of ulcers at the heel is lower than that at the toes, and the location of the ulcers on the heel is one of the factors inhibiting wound healing.

Heel ulcers in bedridden patients who were hospitalized for another disease were thought to be pressure ulcers; however, some cases were diagnosed with PAD. Nearly three-quarters of the patients with heel ulcer at our hospital had PAD. Heel ulcers with PAD are difficult to heal and require abundant blood flow to heal the wounds (2,3). The rate of wound healing was increased following revascularization for PAD. Therefore, early diagnosis of PAD is an important factor for wound healing. Moreover, dialysis has also been reported as a wound healing delay factor for heel ulcers (7,14). However, the influence of dialysis on wound healing was low at our hospital. Successful revascularization influenced wound healing.

The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial compared the bypass-first or angioplasty-first in a randomized controlled trial of patients with PAD in the United Kingdom, which was published in 2005 considering the method of revascularization (15). There was no significant difference in the short-term results in EVT and bypass for patients with PAD below the inguinal ligament in terms of survival and AFS. However, a 2010 study on the long-term results found that bypass using autologous vein grafts was superior to EVT in patients who survived for more than 2 years after surgery (16). Based on the results of the BASIL trial, it is stated in the American College of Cardiology Foundation/American Heart Association guidelines that bypass should be performed for patients who have autologous veins that can be used and have a prognosis of 2 years or more (17). However, in the BASIL trial, cases with lesions below the knee, and dialysis cases were not included. Therefore, the patient background is slightly different from that of Japan. In Japan, many patients are on dialysis (1 in 378.8 people) (18). The Surgical Reconstruction Versus Peripheral Intervention in Patients with Critical Limb Ischemia (SPINACH) study was a multicenter prospective observational study on the treatment of lower limb ischemia in Japan (19). In this study, nearly half of the patients were on dialysis, and the patient background was similar to that of our study. In this study, there was no significant difference in the 3-year AFS between the two groups. It demonstrated the recommended factors for bypass and EVT; bypass is recommended in those with deep wounds, severe infection, previous minor amputation of the foot, history of revascularization treatment, and bilateral critical limb ischemia. On the other hand, EVT is recommended in those with Hb <10g/dl, DM, renal failure, a history of nonadherence to cardiovascular risk management, and major contralateral amputation.

EVT is less invasive than bypass and is used to treat patients with poor general condition. In the recent years, EVT has become widespread and easy to perform owing to advances in the devices and improvements in technology (20). Iida et al. reported that 73% of the patients in whom EVT was performed in the arterial region below the knee would have restenosis or occlusion within 3 months following surgery (21). Thus, shallow wounds that are expected to heal within 3 months and uninfected wounds are factors to be considered when opting for EVT. Advanced devices, such as drug coated balloons and drug eluting stents, which prevent restenosis with EVT are anticipated in the future (22).

In our study, the bypass group had a significantly higher wound healing rate than the EVT group. In recent years, it has been reported that AFS, with only heel ulcers rather than an entire foot ulcer, is higher with bypass than EVT (12). In the past, we compared the changes in foot blood flow following revascularization using EVT and bypass with SPP at our hospital. EVT and bypass, on an average, increased by 27.8 mmHg and 37.8 mmHg, respectively. Furthermore, in the case of infrapopliteal lesion, the average increase was 28.0 mmHg in EVT and 45.9 mmHg in bypass. Bypass demonstrated a significant increase in the blood flow (23). However, in the EVT group, there were cases where the blood flow did not increase adequately to heal the wound even following a successful revascularization. In patients with PAD with deep ulcers, a bypass that is more invasive but durable and can provide abundant blood flow over a long period of time is preferred if the bypass selection criteria are met. Berceli et al. reported that bypass grafts to the dorsalis pedis artery provide substantial perfusion to the posterior foot, and the healing rates of revascularized heel ulcers is excellent and comparable with those observed for ischemic forefoot pathology (24). In the case of bypass, our study suggested that wound healing can be expected if the distal blood vessel can be connected to the dorsalis pedis artery even when it cannot be connected to the posterior tibial artery, which is the blood vessel supplying the heel. Since the report is from a single facility at our hospital, there is no bias related to the differences in the revascularization techniques or treatment policies between facilities. It is necessary to choose a method of revascularization considering the merits and demerits of surgery after evaluating the condition of the blood vessels and the general condition of each case.

Based on the stage of the ulcer, the deeper the ulcer, the longer the wound healing time tended to be with or without PAD. The wound healing time of deep ulcers in the PAD (r +) group and the non-PAD group were 133 (IQR 80－212) and 91 (IQR 61－220) days, respectively. In cases with PAD (r +), aggressive debridement surgery was performed following successful revascularization. Therefore, PAD (r +) cases required additional treatment and tended to take longer than non-PAD cases. It is not possible to simply compare the two. However, we consider that this data will provide an indication of the treatment for heel ulcers. Heel ulcers with PAD reportedly have an average wound healing time of 4－5 months, and the wound healing requires up to 6 months of vascular patency (3,14,25). Our findings are in agreement with those. The wound healing time of the PAD (r +) group was approximately 4.5 months. In particular, the wound healing time for stage IV ulcers was nearly 6 months. The wound healing time with bypass and EVT cases was 128 (IQR 93－174.5) days and 155.5 (IQR 86－237.5) days (P = 0.459). Although there was no significant difference, EVT cases tended to take a longer time to heal than bypass cases.

Many patients had heel ulcers with PAD (73.5%). The wound healing rate of the heel ulcer is low, and the wound healing rate is further reduced in patients with PAD. For heel ulcers with PAD, revascularization is an important factor. Therefore, screening for PAD is important in patients with heel ulcers. The wound healing time for the PAD group, which has many deep ulcers, is approximately 4.5 months and can take longer in some cases. Heel ulcers, which are more difficult to heal than other foot ulcers, are likely to require repeated revascularization before wound healing. Therefore, it is important to check the blood flow with the Doppler ultrasonic stethoscope every day, since any decrease in the blood flow would be detected early leading to prompt revascularization. Restenosis or occlusion of the blood vessels should be suspected if the wound is pale or if healing is stagnant; therefore, it is important to promptly contact the vascular surgeon and treat it. There were many EVT cases at our hospital; EVT has a higher rate of vascular occlusion than bypass. In addition, in some EVT cases, the patency rate of the blood vessels may not reach 100%, and even if EVT is successful, abundant blood flow may not be obtained for wound healing; thus, the wound healing rate was considered to be low. To improve the wound healing rate and shorten the wound healing time, bypass should be considered in patients with ischemic heel ulcer even in cases of dialysis if bypass selection criteria are met.

CONCLUSIONS

Nearly three-quarters of the patients with heel pressure ulcer had PAD. The wound healing rate of the heel ulcer was as low as approximately 30%, and the wound healing rate was further reduced in patients with PAD. It is important to evaluate the blood flow in the lower extremities, since patients with heel pressure ulcers often have PAD. Revascularization in the cases of PAD is important for wound healing and it is also important to check for decreased blood flow during treatment. Bypass surgery, which provided abundant blood, had a shorter wound healing time and a higher wound healing rate than EVT. Therefore, for ischemic heel ulcers, bypass should be considered if bypass selection criteria are met.

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