■ 原　著　日血外会誌 14：83–89，2005

Limb Salvage Achieved by Paramalleolar Bypass with Topical Treatment

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Abstract: Objectives: Among several procedures to treat critical limb ischemia, bypass surgery has the most potent effects to cure ischemic ulcer or gangrene. However, it is not easy to cure ischemic tissue loss in patients with diabetes (DM) because of infection and wound healing disorder, even if enough blood supply is established by bypass surgery. The importance of topical treatment after bypass surgery remains to be defined.

Patients and Methods: We reviewed medical records of 117 limbs in 109 patients undergoing bypass surgery during the last 10 years for Fontaine's grade IV critical limb ischemia. Sixty-nine percent of patients had diabetes, and 29% of patients had hemodialysis-depending renal failure (HDRF). Aorto-femoro-crural bypass was the most common procedure in the non DM (NDM) group, while femoro-paramalleolar bypass was performed most frequently in the DM group. After bypass surgery, vacuum assisted closure methods (VAC) as well as basic fibroblast growth factor were applied to the open wound, aiming to promote granulation. Thirty-nine percent of limbs needed minor amputation, with or without skin grafting, and 4 limbs underwent free flap transfer (3 rectus flaps and one latissimus dorsi flap).

Results: There were two operative deaths due to cerebral vascular events. Five limbs underwent major amputation within the perioperative period. Two of them already had extensive necrosis, and 3 other limbs were lost due to uncontrollable infection, despite the patency of the graft. Eighty-eight percent of ischemic ulcers or gangrene (83% in NDM group and 90% in DM group) were finally cured without major amputation. There was no statistical difference of the cumulative limb salvage rate between the NDM group and the DM group (90% and 93%, respectively at 36 months). However, DM patients still needed a much longer period to cure their ischemic ulcer or gangrene compared with NDM patients (103 ± 90 vs. 41 ± 24 days, $p = 0.0067$). Among DM patients, it took a long time to cure wound in patients with HDRF (139.4 ± 111 days).

Conclusion: To treat critical ischemia, not only bypass surgery but also adequate topical treatment is important. Further development of topical treatment is essential to cure ischemic foot in a minimum time and minimum amputation in diabetic patients, especially those with HDRF. (Jpn. J. Vasc. Surg., 14: 83–89, 2005)

Key words: Critical limb ischemia, Pedal bypass, Vacuum-assisted closure, Basic fibroblast growth factor, Free flap transfer

Introduction

Diabetic atherosclerosis is major cause of ischemic limb loss. Among the several procedures to treat critical limb ischemia (CLI), bypass surgery supplying enough blood to ischemic tissue directly is most effective.[1)] However, CLI especially in patients with diabetes mellitus (DM) has complex patho-physiological features such as disorders of microcirculation, immunological reaction and wound healing. Bypass surgery can solve macroangiopathy, though other features of DM still resist treatment. Therefore if bypass graft is successfully

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Received: Oct. 22, 2004
Revision accepted: Feb. 10, 2005

Table 1 Clinical characteristics of patients undergoing bypass surgery for ischemic ulcer or gangrene

	NDM group	DM group	p value
Patients	34	75	
Limbs	35	82	
Age			
Mean±SD	71.9±10.2	66.7±9.7	p<0.05
Range	43–89	39–86	
Male gender	82.4%	80.0%	N.S.
Risk factor			
Hypertension	61.8%	57.3%	N.S.
Coronary artery disease	14.7%	33.3%	p<0.05
Symptomatic cerebral infarction	14.7%	13.3%	N.S.
Hemodialysis-dependent renal failure	11.8%	37.3%	p<0.01

established, it is still not easy to control infection and to cure ischemic ulcer or gangrene in DM patients. In this study, we evaluated the efficacy of bypass surgery as well as topical treatment and surgical procedures after bypass surgery.

Patients and Methods

We reviewed the medical records of 117 limbs in 109 patients undergoing bypass surgery from 1994 to 2003 for CLI with ischemic tissue loss. The critical ischemic limbs classified into Fontaine's grade Ⅲ were excluded in this study. Sixty-nine percent of patients had DM. In order to clarify the significance of DM in terms of surgical strategy and results, the patients were divided into the DM group and the non-DM (NDM) group.

Patients and ischemic limbs: Table 1 demonstrates the preoperative clinical characteristics of the patients. Hemodialysis-dependent renal failure (HDRF) and coronary arterial disease including significant arterial stenosis, a history of intervention, and signs of old myocardial infarction were seen more frequently in the DM group. DM patients were relatively younger, but they had relatively higher risk of cardiovascular events than NDM group. Regarding the status of ischemic ulcer or gangrene of limbs, DM patients showed a tendency to have relatively extensive and deep tissue loss when compared to NDM patients. Sixty percent of ulcer or gangrene lesions in the NDM group were localized in toes, while only 31% of ulcer or gangrene lesions in the DM group were limited to toes, most of them had already extended beyond the metatarsophalangeal joint or more proximal. Bacterial culture revealed that 62% of limbs in the NDM group had bacteria positive in their ulcer or gangrene at the first visit, while 75% of limbs in the DM group were bacteria positive. Although there was no statistical difference between DM and NDM group in terms of frequency of positive bacterial culture, antibiotic-resistant strains like methicillin resistant staphylococcus aureus (MRSA) were more frequently found in the DM group.

Preoperative evaluation: Evaluating the infection of ischemic tissue loss, diagnosis of arterial occlusive disease, and evaluating risk factors of patients are all important, and should be done as fast as possible for patients with CLI. To evaluate infection of ulcers or gangrene, bacterial culture as well as plain-film radiograph of the foot was performed. The plain-film was important to diagnose soft tissue gas, deformity of bone, as well as osteomyelitis. When osteomyelitis was suggested by the plain-film, magnetic resonance imaging (MRI) was useful to confirm the diagnosis of osteomyelitis. Fifteen percent of limbs in the DM group underwent bed-side debridement or minor amputation prior to bypass surgery, to avoid spreading of infection. Diagnosis of localization and extension of arterial disease was done by intra-arterial digital subtraction angiography (IADSA) or magnetic resonance angiography (MRA) in most cases. Although the distal target artery was invisible on preoperative evaluation in 5 cases, intraoperative angiogram, or "blind" exposure of paramalleolar arteries were useful to find out target artery

Table 2 Procedures of bypass surgery and outflow target arteries of infrainguinal bypasses

	NDM group (n=35)	DM group (n=82)
Procedures of bypass surgery		
Ao-F (or Ilio-F) bypass	2 (5.7%)	1 (1.2%)
Ao-F -Distal bypass	15 (42.9%)	24 (29.3%)
F-Distal bypass	8 (22.9%)	53 (64.6%)
Extra-anatomic bypass*	7 (20.0%)	2 (2.4%)
PTA+Distal bypass	3 (8.6%)	2 (2.4%)
Distal anastomotic site of distal bypasses		
Popliteal (above knee)	4 (14.3%)	4 (5.1%)
Popliteal (below knee)	7 (25.0%)	5 (6.4%)
Crural	11 (39.3%)	12 (15.4%)
Paramalleolar of pedal	6 (21.4%)	57 (73.1%)

*Extra-anatomic bypass includes axillo-femoral and femoro-femoral bypass.

and establish anastomosis. For cases with calcified arteries, plain-film radiograph of the foot was essential to search calcification-free segments as suitable anastomotic site. To clarify risk factors of patients is important to serve secure surgery. Patients routinely underwent carotid echogram as well as dipyridamole thallium scintigraphy or dobutamine stress echocardiography. Only two patients who had critical coronary artery disease underwent percutaneous cardiac intervention prior to peripheral bypass surgery, while most of patients with coronary arterial disease already had history of percutaneous coronary intervention or coronary artery bypass grafting.

Bypass procedures: In order to cure ischemic limbs as quick as possible and salvage limbs as much as possible, we have aimed complete revascularization. The bypass procedures and outflow arteries are listed in **Table 2**. Most of patients in the NDM group had femoro-popliteal lesion concomitant with aorto-iliac lesion, thus, aorto-femoro-distal bypass was the most common procedure. On the other hand, most patients in the DM group had a crural arterial lesion, so femoro-distal bypass was most frequent (65% of limbs). The most common distal anastomotic site for femoro-distal bypasses in NDM group was crural or below-knee popliteal artery, while it was the paramalleolar artery in the DM group. Vein grafts were essential for bypasses to below-knee or more distal arteries. Among 93 vein grafts, 53 grafts were used in-situ and 40 grafts were used in reversed fashion. If the greater saphenous vein could not be used, the lesser saphenous vein, arm vein, deep vein, or their veno-venous composite were used. For bypass to severely calcified arteries, balloon catheters were employed to control arterial back flow. For five cases whose graft flow was insufficient because of poor run-off, a fine catheter (Argyle® PI catheter, 28 gauge) to infuse prostaglandin E_1 (PGE_1) continuously through the vein graft was inserted into the vein graft to avoid early graft occlusion as well as to improve peripheral microcirculation.

Post-bypass procedures: After bypass surgery, anti-platelet agents were administered all patients. However, anticoagulants were used only in patients with hypercoagulability such as deficiencies of antithrombin III, protein C, S, abnormality of plasminogen, fibrinogen as well as lupus anticoagulant. Patients with digital gangrene underwent toe or ray amputation. Extensive gangrene involving the foot was treated with persevering debridement and applying ointment such as sulfadiazine silver until the number of bacteria decreased. When the results indicated no or decreased bacteria, the vacuum-assisted closure method (VAC) as well as applying growth factor spray such as basic fibroblast growth factor (Kaken Pharmaceutical, Japan) were employed, aiming to facilitate tissue growth. The VAC system was developed in the U. S. A., converting the open wound into a controlled closed wound by applying a sterile foam.[2, 3] The foam is

Table 3 Surgical procedures after bypass surgery. Limbs with still open wounds or major amputation were excluded.

Surgical procedure after bypass surgery	NDM group	DM group
Bypass grafting alone	19 (63.3%)	25 (33.8%)
Bypass+Minor amputation	6 (20.0%)	34 (45.9%)
Bypass+Skin grafting	3 (10.0%)	13 (17.6%)
Bypass+Free flap transfer	2 (6.7%)	2 (2.7%)

attached to evacuation tube, which in turn is connected to the vacuum source. The foam was then wrapped with sterile film, and drained with negative pressure of approximately 100 mmHg. After formation of good granulation tissue, 16 limbs underwent skin grafting. Since limbs in the DM group had more extensive tissue loss, more than half of the limbs needed minor amputation with or without skin grafting. Three patients with extensive loss of their forefoot underwent rectus flap transfer, and one patient with extensive necrosis of dorsal foot underwent latissimus dorsi flap transfer on (**Table 3**).

Follow-up and evaluation: All grafts were followed by a rigorous surveillance protocol including by means of physical examination, segmental blood pressure measurement, and duplex scanning. Follow-up was scheduled at 1 month, 3 months, 6 months, 12 months, and every 6 months thereafter.

Statistical analysis: Data were expressed as means ± standard deviation, and unpaired t-test and chi-square test were performed with the aid of Statview software (version 5.0 for Windows, SAS Institute Inc., NC, U. S. A.). Primary and secondary graft patency and the limb salvage rate were calculated using the life-table method. Life tables were compared by the log-rank test.

Results

There were two operative deaths due to cerebral infarction and cerebral hemorrhage (one in the NDM group, the other in the DM group). The operative mortality rate within one month in the NDM group and DM group were 2.9% and 1.3%, respectively ($p = 0.56$; not significant).

Although 7 vein grafts (4 grafts in the NDM group, 3 grafts in the DM group) became occluded within the first 30 days after operation, 6 grafts were salvaged. The main cause of early graft failure was poor quality vein in the NDM group, while it was technical error such as residual valve and inadequate selection of the anastomotic site in the DM group. One graft occluded due to poor run-off could not be salvaged. There was no early failure of an artificial graft implanted in the aorto-iliac region. The primary cumulative patency rates of femoro-distal bypasses were 64% in the NDM group, 75% in the DM group, respectively at 36 months. Fifteen grafts (5 grafts in the NDM group and 10 grafts in the DM group) were failed or failing due to intimal hyperplasia, and 11 grafts were successfully revised. The secondary cumulative patency rate of femoro-distal bypasses was 87% in the NDM group, 93% in the DM group, respectively at 36 months. There was no statistical significance between the NDM and DM groups in terms of graft patency.

Five limbs underwent major amputation within the perioperative period. Two of them in the NDM group already had extensive necrosis beyond the foot joint, so below-knee amputation was performed after extra-anatomical bypasses. Three other limbs belong to DM group were lost due to uncontrollable infection, despite patent paramalleolar bypasses. The outcome of limbs at 6 months after the bypass operation was summarized in **Figure. 1**. Five limbs were lost as described above, while 96 limbs were completely healed within 6 months. The VAC method was highly effective to facilitate the growth of granulation tissue, which sometimes covered the surface of exposed tendons and bones (**Fig. 2**). Although 10 limbs still had the open wound at 6 months after bypass surgery, 7 of the 10 limbs were cured completely thereafter, by employing VAC, fibroblast growth factor, as well as plastic technique including skin grafting and free flap transplantation. Finally 88% of ischemic ulcers or gangrene (83% in NDM group and 90% in DM group) was cured with-

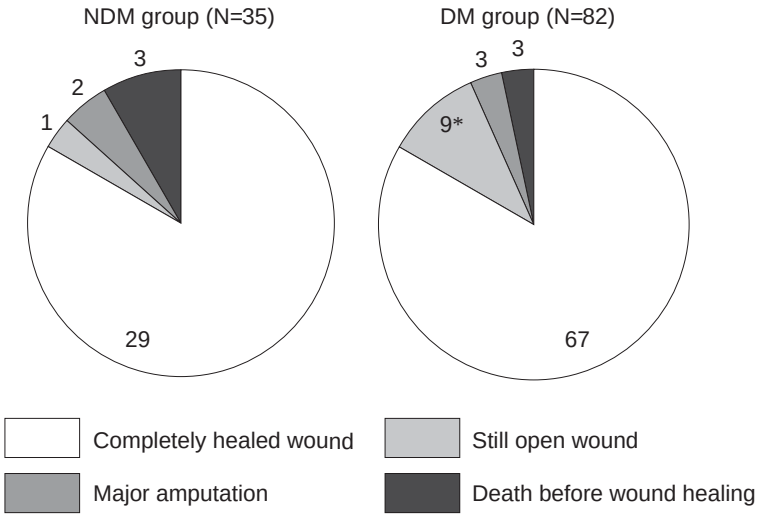

Fig. 1 Prognosis of critical ischemic limbs with tissue loss.
*Nine limbs still had open wounds at 6 months after bypass operation, though 7 of the 9 limbs were finally cured thereafter.

Fig. 2 Effects of vacuum-assisted closure method (VAC) in a 53-year-old man with diabetic gangrene. A: Appearance of gangrene as admission in our hospital. The infection was already spreading to midfoot. Bacterial culture revealed, he was MRSA positive. B: Wound at 3 weeks after femoro-terminal posterior tibial bypass. Most necrotic tissue was already debrided, though tendons and bone were exposed. MRSA was still positive but decreased. VAC was applied at this time. C: Wound at 3 weeks after applying VAC. Most of the wound area, including the tendon, was covered with good granulation. The exposed bone (arrowhead) was also almost covered and ready for skin grafting. D: View at 2 weeks after skin grafting. The wound completely healed.

out major amputation. Although most limbs were salvaged by bypass surgery with topical treatment, it still took a long period to cure their ischemic ulcer or gangrene, especially in DM patients (**Fig. 3**). The time required to cure the wound in the NDM group and DM group were 41 ± 24 days and 103 ± 90 days, respectively ($p = 0.0067$). Among the patients in the DM group, it took much longer to cure ischemic tissue loss in hemodialysis dependent patients compared to non-hemo-

dialysis dependent patients (140 ± 111 days vs. 75 ± 62 days, p = 0.0077). The cumulative limb salvage rate of NDM and DM group was 90% and 93%, respectively at 36 months (**Fig. 4**). In DM patients, the cumulative limb salvage rate of hemodialysis dependent patients was worse than that of non-dialysis dependent patients but there was no statistical significance (88% vs. 96% at 36 months, p = 0.082).

To evaluate the efficacy of aggressive limb salvage, we investigated the QOL of patients. Most patients whose limb salvaged recovered their walking ability, as long as their heels were spared. Among 4 limbs who underwent free flap, 3 of them can walk without prostheses, and one of them is now under rehabilitation.

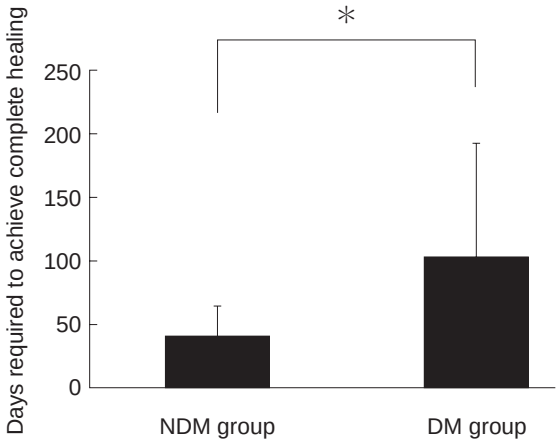

Fig. 3 Time required to cure ischemic wounds. Limbs which were still open or already underwent major amputation were excluded from this analysis.
*p=0.0067.

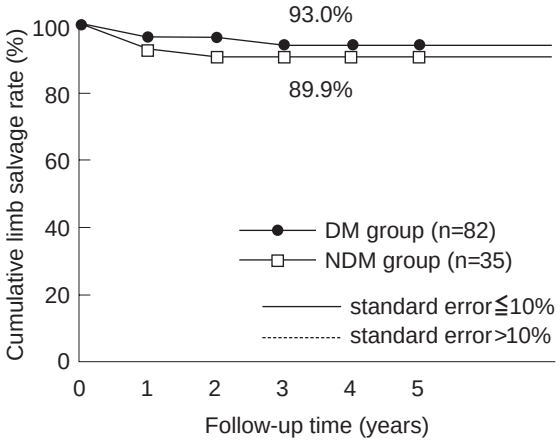

Fig. 4 Cumulative limb salvage rate of all limbs. There is no statistical difference between the NDM group and the DM group.

Discussion

Recovery of walking ability is not easy for the amputated limb with residual ischemia, especially in elderly patients, because of the weight of prostheses, ischemic pain of the stump, and ulceration of skin attached to prostheses. In most elderly patients who undergo major amputation not only their QOL but also their prognosis of life deteriorates.[4, 5] Therefore we have aimed limb and foot salvage as much as possible. The bypass surgery provides immediate and strong effects, and the effects last for a long time. Many reports describe potent effects of paramalleolar bypass for diabetic atherosclerosis.[6–9] Some guidelines for diabetic gangrene recommend bypass surgery.[10] In our institution, we have pefomed paramalleolar or pedal bypass since 1983. Most limbs were salvaged by bypass surgery. However, in some cases especially with DM and HDRF, it took a long time to cure gangrene. Bacterial culture revealed that the strains of bacteria have changed, and become more antibiotic-resistant, in proportion to prolongation of the healing time. In two cases, limb were lost due to infection despite patent bypass grafts. This clinical experience reveals that it is important how fast the ischemic ulcer or gangrene can be cured. Rapid healing of chronic wounds could result in decreased infection and earlier restoration of function. Otherwise, infection might spread proximally or deeply, which could result in osteomyelitis, and loss of walking ability because the period of bed stay was too long. Therefore, in this study, we emphasized the importance of topical treatment before and after bypass surgery. Adequate debridement, drainage, and routine bacterial culture are certainly important.[10] Control of the blood sugar level in DM patients is also important to control infection and promote wound healing. Recently VAC was developed to build up granulation tissue rapidly. A prospective randomized trial of VAC versus standard therapy of chronic nonhealing wounds revealed that VAC therapy promotes faster healing with healthy granulation tissue compared to standard wet-moist dressing.[2] It is speculated that applying negative pressure removes excessive fluid from the wound, which in turn

increases local blood perfusion, and stimulates the growth of granulation tissue to obtain closure.[3] Growth factors, such as recombinant basic fibroblast growth factor spray, are also speculated to be effective to facilitate wound healing, even in DM patients. Employing the VAC system as well as growth factors after bypass surgery are both very effective to develop granulation tissue rapidly, and also contribute not only to minimizing the time to cure, but also to salvaging the foot as much as possible. Although the limb salvage rate in DM patients is thought to be worse than that in NDM patients, our data indicated that the limb salvage rate was not significantly different in th two groups. These data suggest that development of topical treatment contributed to improve the limb salvage rate in DM patients. Procedures of plastic surgery such as skin grafting and musculocutaneous flap transfer are also useful to avoid major amputation and save limbs and feet as much as possible. The musculocutaneous flap transfer is the ultimate procedure for extensive tissue loss with exposed tendon or bone.[11, 12]

One of the most important points is investigating the efficacy of aggressive foot salvage on the QOL of patients. Even if patients who have DM or HDRF with CLI have a short life span, considering their QOL should be very important. We are now investigating the QOL of patients by means of the SF-36 and Hasegawa's dementia score. Preliminary data suggests that salvaging limbs leads to recovery of QOL, to promote not only walking activity and social function but also mental and intrinsic activity.

In conclusion, complete revascularization by bypass surgery with adequate post-operative care such as elaborate topical treatment and plastic surgical procedures can achieve satisfied limb salvage. There are no significant differences between the DM group and NDM group in terms of graft patency and limb salvage rate. There has been some progress in topical treatment such as recombinant growth factors as well as the VAC system, though it still takes a long time to cure ischemic ulcer or gangrene in DM patients. Further development of topical treatment is essential to cure ischemic feet as quickly as possible and to salvage the length and function of the foot as much as possible in diabetic patients, especially those with HDRF.

References

1) TASC working group: Management of peripheral arterial disease: Transatlantic inter-society consensus. J. Vasc. Surg., **31**: S192-S273, 2000.

2) Joseph, E., Hamori, C. A., Bergman, S., et al.: A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. Wounds., **12**: 60-67, 2000.

3) McCallon, S. K., Knight, C. A., Valiulus, J. P., et al.: Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. Ostomy. Wound. Manage., **46**: 28-34, 2000.

4) Hobson, R. W., Lynch, T. G., Jamil, Z., et al.: Results of revascularization and amputation in severe lower extremity ischemia: a five-year clinical experience. J. Vasc. Surg., **2**: 174-185, 1985.

5) TASC working group: Management of peripheral arterial disease: Transatlantic inter-society consensus. J. Vasc. Surg., **31**: S15-S34, 2000.

6) Shah, D. M., Darling, Ⅲ. R. C., Chang, B. B., et al.: Is long vein bypass from groin to ankle a durable procedure? An analysis of a ten-year experience. J. Vasc. Surg., **15**: 402-408, 1992.

7) Harrington, E. B., Harrington, M. E., Schanzer, H., et al.: The dorsalis pedis bypass-moderate success in difficult situations. J. Vasc. Surg., **15**: 409-416, 1992.

8) Gloviczki, P., Bower, T. C., Toomey, B. J., et al.: Microscope-aided pedal bypass is an effective and low-risk operation to salvage the ischemic foot. Am. J. Surg., **168**: 76-84, 1994.

9) Pomposelli, F. B., Kansal, N., Hamdan, A. D., et al.: A decade of experience with dorsalis pedis artery bypass: Analysis of outcome in more than 1000 cases. J. Vasc. Surg., **37**: 307-315, 2003.

10) Frykberg, R. G., Armstrong, D. G., Giurini, J., et al.: Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. J. Foot. Ankle Surg., **39**: S1-60, 2000.

11) McCarthy, Ⅲ. W. J., Matsumura, J. S., Fine, N. A., et al.: Combined arterial reconstruction and free tissue transfer for limb salvage. J. Vasc. Surg., **29**: 814-820, 1999.

12) Illig, K. A., Moran, S., Serletti, J., et al.: Combined free tissue transfer and infrainguinal bypass graft: An alternative to major amputation in selected patients. J. Vasc. Surg., **33**: 17-23, 2001.