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Clinical outcomes of patients with peripheral artery disease and lower extremity wounds based on a predetermined intention-to-treat strategy

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ABSTRACT

Achieving healing in patients with peripheral artery disease and lower extremity wounds represent a significant clinical challenge. Important outcome measures that define a successful therapeutic approach include wound healing rate, time to heal, and recurrence with time. This article reviews our experience managing a peripheral artery disease patient cohort at a Veterans Affairs medical center based on the initial clinical evaluation stratification and prospective enrollment into a predetermined treatment strategy.

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1. Introduction

Peripheral artery disease (PAD) is defined as progressive stenosis or occlusion of the extremity arteries primarily due to underlying atherosclerosis [1]. It has become a global problem in the 21st century, affecting 8 to 12 million people in the United States [2,3]. This disease can range from asymptomatic to critical limb ischemia. A recent consensus statement by the Trans-Atlantic Inter-Society Consensus on Management of Peripheral Artery Disease suggests that ulcers and gangrene can occur with ankle pressure of <70 mm Hg or toe pressure <50 mm Hg [4]. However, tissue loss can occur with higher values. It has been suggested that this subgroup of patients with "subcritical limb ischemia" and tissue loss have a relatively lower risk of limb loss compared to those with critical limb ischemia [5]. Earlier studies have reported that this group of patients has a high probability of healing without revascularization when a multidisciplinary approach is combined with aggressive wound care [5–8].

Furthermore, previously published studies have reported a diagnostic advantage of transcutaneous oxygen measurement in the evaluation of patients with arterial insufficiency. This measurement can help to determine the need for revascularization in patients with PAD and lower extremity wounds [6,9–11]. Following Veterans Health Administration guidelines [12], we established the Prevention of Amputation in Veterans Everywhere (PAVE) multidisciplinary team at our VA health care system. In this report, we detail patient outcomes and wound healing rates based on enrollment in a predetermined intent-to-treat strategy with and without lower limb revascularization.

2. Materials and methods

This study was a retrospective review of a single-center prospectively maintained PAVE database at the Loma Linda VA Hospital from January 2006 to November 2014. This database was designed to evaluate the long-term outcomes

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of veterans presenting with PAD and nonhealing wounds (Rutherford class V–VI). Our team is composed of vascular surgeons, podiatrists, a pharmacist, a physical medicine and rehabilitation physician, and a nutritionist. During weekly meetings, the team reviews and stratifies all cases of patients presenting with PAD (ankle-brachial index [ABI] <0.9) and tissue loss in the lower extremities. The patients were enrolled into the following treatment groups: revascularization, medical management without revascularization, primary amputation, and palliative limb care.

The decision to place a patient into a particular treatment group was based on the severity of ischemia (ABI, transcutaneous oxygen measurement [$TcpO_2$]), comorbidities, extent of tissue loss, and functional status of the patient. $TcpO_2$ are measured in the hind foot or forefoot. $TcPO_2$ values in the distribution of tissue loss were utilized. Patients with a low ABI (<0.9), $TcpO_2$ <30 mm Hg, and those considered physiologically suitable for either endovascular or open procedures, were placed into the revascularization group. If at presentation, the patient had a $TcpO_2$ >30 mm Hg (indicating potential ability to heal without revascularization), a wound care–only approach was be attempted, predicated on close follow-up. This group is known as the medical–no revascularization management group. Primary amputation was performed when extensive foot-tissue loss precluded functional podiatry amputations, no anatomic target vessels are identified, or patient is too high risk to undergo intervention. Patients that presented with $TcpO_2$ <30 mm Hg and who are not candidates for either revascularization or primary amputation are allocated into the palliative limb care group when they have short expected survival, no rest ischemic pain, and the wound is not severely interfering with quality of life (eg, no uncontrolled odor, discharge, or infection). This analysis explored the long-term outcomes and wound care strategies utilized in the revascularization and conservative ischemic groups.

Criteria for exclusion from this analysis were concomitant venous disease, determined by the appearance and location of the wound and the consensus of treating physicians, and death before 6 months without complete resolution of the wound. All patients were prospectively entered into a Microsoft Access Database. The primary endpoints were complete wound healing (100% epithelialization without discharge) and mean time (months) to complete wound healing. Patients were classified as healed, failure to heal, or active. Failure to heal was defined as lack of progression of the wound during follow-up, without signs of active healing, or development of pedal sepsis. If multiple wounds were present in a single extremity, complete healing was defined as resolution of all wounds in that extremity. If the patient presented with wounds in both extremities, each extremity was analyzed separately. The reappearance of a foot lesion after the primary wound had healed was considered a wound recurrence. Secondary outcomes included freedom from wound recurrence, need for late revascularization, and overall survival.

Descriptive statistics were expressed as mean ± standard deviation and median. Outcomes are presented as number and proportions. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (released 2013, IBM Corp, Armonk, NY). Chi-square test was used to evaluate the univariate predictor of wound healing between patients who healed and those who did not heal, and all P values <.05 were considered significant. Kaplan-Meier life tables were used to analyze mortality. The study was approved by the Institutional Review Board at the Jerry L. Pettis Memorial Veterans Medical Center in Loma Linda, CA.

3. Results

From January 2006 to November 2014, a total of 709 limbs with 867 wounds were enrolled in the PAVE registry Overall, 258 limbs (36.3%) with 302 wounds were allocated into the medical–no revascularization group, 271 (38.5%) limbs with 337 wounds were placed into the revascularization group, 68 (9.5%) limbs with 89 wounds were stratified to primary amputation, and 112 (15.7%) limbs with 139 wounds were allocated into palliative limb care. Mean follow-up was 33.6 months (range, 1.5 to 104 months). Two hundred and eighteen limbs with 266 wounds in the revascularization group and 203 limbs with 231 wounds in the conservative cohort met inclusion criteria. The patient's demographic characteristics and risk factors for both revascularization and conservative groups are presented in Table 1, and wound type and location are shown in Table 2. Wound-specific stratification at index visit included foot x-ray, baseline measurements, and determination of whether a podiatric intervention would be the most efficient approach to healing. If primary surgical closure was not feasible using our basic wound care algorithm, includes, weekly visits for the first month and biweekly thereafter. The expected wound trajectory is decreased of the wound surface by 50% in 4 weeks in an optimized wound environment (absence of soft tissue or bone infection, edema control, proper nutrition, off-loading). All patients received a course of vitamin/mineral replacement (zinc sulfate 220 mg by mouth daily for 2 weeks, vitamin C 500 mg by mouth daily [except in end-stage renal disease], multivitamin supplement or renal tab daily, vitamin D 2000 IU daily, vitamin A 25,000 IU [if patient is on steroids]) and protein supplements if needed. At each visit, the need for sharp, chemical (collagenase), or autolytic debridement (medical grade honey) was recorded. Selection of dressings was based on wound moisture and peri-wound care with zinc ointment. If the trajectory of the wound healing was not positive, we then switched to our advanced wound care protocols (ie, split thickness skin grafts, Apligraft, Integra, Epifix, Dermagraft, and negative pressure wound therapy) (Table 3).

Overall wound healing rate for patients stratified to the medical–non-revascularization group was 76.7%. Mean time to heal was 4.1 months, with a median of 3 months. Patients presenting with an ulcer achieved an 80% healing rate, and those presenting with gangrene achieved only a 58% healing rate. In the revascularization group, the wound healing was documented at 67%, with a mean time to heal of 6.4 months with a median of 5 months (Table 4). Predictors of successful healing included ulcer at index presentation for both revascularization and conservative groups. Conversely, gangrene at index visit negatively impacted wound healing for both