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Effect of Systemic Urokinase Infusion After Lower Limb Percutaneous Transluminal Angioplasty on Limb Salvage Rate in Patients with Late-stage Critical Limb Ischemia

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WHAT THIS PAPER ADDS

This study evaluated the effect of systemically administered urokinase (UK) for 5 days after percutaneous transluminal angioplasty with or without stent on the reduction of the rate and level of amputation in patients with critical limb ischemia (CLI) with tissue loss. It was postulated that patients with CLI may have increased clot load at tissue level due to decreased flow with diseased pedal arteries, and embolization due to the intervention. The results showed that systemic administration of UK may reduce the requirement for major amputations (especially for infrapopliteal interventions). However, these findings need to be confirmed in a randomized prospective study.

Objective: To evaluate the effect of systemically administered urokinase (UK) after percutaneous transluminal angioplasty with or without stent (PTA ± stent) on the reduction in the rate and level of amputation in patients with critical limb ischemia (CLI) with tissue loss.

Methods: This was an observational, nonrandomized, retrospective study of 183 Taiwanese patients with Rutherford stage 5 or 6, and Fontaine stage 4 lower extremity CLI. Patients received either PTA ± stent or PTA ± stent + UK infusion (250,000 IU, daily for 5 days). PTA of the iliac, femoral, anterior tibial artery, posterior tibial artery, and peroneal arteries was included. Amputation was classified as minor, with direct wound healing, and minor amputation or surgical debridement of toes and major, with below- (BKA) and above-knee amputation (AKA).

Results: In groups of patients with comparable baseline characteristics, 85 and 90 patients received PTA ± stent and PTA ± stent + UK, respectively. There were 24 major limb amputations performed. A significant majority (20/24 (83.3%) were performed in patients who did not receive adjuvant urokinase, compared with 4/24 (16.7%) of patients who did receive urokinase ($p = 0.000287$). There was a significant increase in the limb salvage rate for infrapopliteal lesions in patients treated with PTA + UK (12/72 with UK; 60/72 without UK; $p \leq .0001$). Intracranial hemorrhage ($n = 1$) and bleeding at the inguinal puncture site ($n = 2$) were reported in the PTA ± stent + UK group. Eight deaths (one in the PTA ± stent + UK group; seven in the PTA ± stent) occurred during the study.

Conclusion: Systemic administration of UK with the PTA ± stent procedure may reduce the requirement for major amputation in patients with CLI with tissue loss (Rutherford 5 or 6). The difference is more pronounced in patients undergoing infrapopliteal interventions. However, these findings need to be confirmed in a randomized prospective study.

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INTRODUCTION

Percutaneous transluminal angioplasty (PTA) for dilatation of a stenotic lesion is a well established endovascular procedure for lower limb atherosclerosis.[1] Femoropopliteal and infrapopliteal interventions have been increasingly used in the last decade, especially in patients with significant comorbidities,[2,3] and in those who have acute or subacute presentations with significant clot loads in their occluded arterial segments.[4–6] Significant microembolization occurs during endovascular interventions, most of which goes undetected.[7] In some studies, low-dose systemic urokinase (UK) was used alone, without any intervention in patients with diabetes in order to improve microcirculation and

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thereby the limb salvage rates, suggesting that there may be an increased clot load at the microcirculation level in these patients.[8,9] It was postulated that patients with critical limb ischemia (CLI) may have increased clot load at tissue level due to decreased flow with diseased pedal arteries, and embolization due to the intervention. Therefore, use of systemic UK as an adjunctive method to improve blood flow at the tissue level following endovascular interventions was planned to theoretically decrease the clot load at tissue level.

Here, the findings of a large, preliminary, observational, retrospective study that evaluated the effect of infusion of UK after PTA ± stent in patients with CLI with tissue loss on the rate of limb salvage are reported.

MATERIALS AND METHODS

Study design

This observational, nonrandomized, retrospective study evaluated patients with CLI with tissue loss from June 2009 to May 2012 in Kaohsiung Chang Gung Memorial Hospital, Taiwan. The patients were divided into two groups. The first group received PTA ± stent, while the second was treated with PTA ± stent followed by the systemic intravenous (IV) infusion of UK (PTA ± stent + UK). The administration of UK was initiated in March 2010; therefore, the first 50 patients treated and included in the study did not receive UK. Thereafter, all patients were treated with UK; however, patients with a contraindication to UK or those who did not consent to the use of UK were placed in the PTA ± stent group. All patients were treated with either balloon angioplasty only and/or with a bail-out stent following balloon angioplasty.

Patients

Adult male or female patients with CLI with tissue loss of the lower extremity (Rutherford classification stage 5 or 6, and Fontaine classification stage 4) were included.[1,10,11] Patients with angiopathic or angioneuropathic diabetic foot lesions, limbs with poor wound healing status after minor amputation of foot or toes, and foot wounds caused by angiopathy (confirmed by angiography) were also included if they had an ankle–brachial index (ABI) of <0.7 (without uncontrolled hypertension) or severely calcified vessels with ABI of >1.5 (where stenosis cannot be evaluated), a dampened or partially pulsatile pulse–volume curve, and/or existing toes that were silent or partially pulsatile. Patients were excluded from PTA ± stent + UK if the infusion of UK was contraindicated, such as in those with untreated proliferative retinopathy, an allergy to UK, a cerebrovascular episode within 6 months, uncontrolled hypertension, hemorrhagic diathesis, a plasma fibrinogen level <200 mg/dL, or gastrointestinal bleeding within 3 months. Other exclusion criteria included the need for oral anticoagulation, mental disorders, pregnancy, or participation in another study. Patients with neuropathic diabetic foot lesions without angiopathy were also excluded after angiography.

Treatments

PTA procedure. Balloon angioplasty was performed using a Pacific 0.018 wire system (Medtronic Invatec, Minneapolis, MN, USA) or ATB ADVANCE 0.35 wire system (Cook Medical, Bloomington, IN, USA). The catheter was inserted to the site of narrowing through a routine contralateral femoral puncture with retrograde crossover access. Diagnostic angiography was performed to confirm the target lesion and the choice of treatment. If the sheath was able to pass beyond the lesions in the iliac or superficial femoral arteries (SFA), the lesion below the knee was treated first to achieve, at least, a two-vessel distal runoff. The SFA or iliac lesions were treated thereafter. In all cases, we treated the infrapopliteal lesion first, except when there was a total occlusion of the SFA. After clearing the infrapopliteal occlusion, the SFA segment was treated to ensure good distal runoff. If possible, antegrade and retrograde flow was assessed using the angiosome concept to create at least two distal runoff vessels (>90% patients). At least one distal runoff was achieved in the remaining cases. A stent (Life stent [Bard PV, Tempe, AZ, USA]; Zilver stent [Cook Medical]; or Maris stent [Medtronic, Minneapolis, MN, USA]) was placed, if considered needed. These stents were mostly bail-out stents for balloon angioplasty causing focal dissection or limited flow or recoil with 50% residual stenosis in the SFA. However, a repeat balloon angioplasty was performed for the below-knee arteries. To assess the limited residual stenosis in the iliac or SFA, and to confirm the two-vessel distal runoff in the below-knee arteries, the result of the PTA procedure was checked by a final angiography. Assessments of wound healing and distal pulsation (using hand-held Doppler) were performed daily during the period of hospitalization. If poor progression of wound healing was observed, ABI was repeated after 2 weeks. If the pulse signal was absent, angiography was repeated to confirm patency of the target lesion. Based on the angiographic findings, endovascular treatment options were assessed by multidisciplinary consensus among angiologists, vascular surgeons, and interventionalists. Minor amputation or debridement was carried out in stages, as required, for the prevention of infection. Thereafter, the decision to perform limb amputation (with possible local rotational flap or intensive wound care), with the aim of maximal limb preservation, was undertaken by a team of vascular surgeons, angioplasty surgeons, and orthopaedic surgeons after obtaining patient consent. Furthermore, below-knee amputation (BKA) was performed before above-knee amputation (AKA). Structured wound care, including wound debridement and moist wound dressings, was provided to every patient. The choice of moist dressing was at the discretion of the surgeon. Patient follow-up lasted until complete healing of the wound was observed or until major amputation was required. The length of hospital stay was recorded.

IV infusion of UK and concomitant medications

Systemic IV UK (Urokinase-GCC Injection 250,000 IU [Green Cross Corporation, Yongin, Korea]) was administered daily