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Influence of Secondary Infection on Amputation in Chronic Critical Limb Ischemia

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Objectives. *To evaluate the influence of secondary infection on major amputation in chronic critical leg ischemia (CLI).*
Design. *Prospective, controlled observational study.*
Materials and Methods. *Sixty-seven patients with CLI and ischemic lesions participated in the study. Presence of infection was defined by clinical, laboratory and radiological criteria. Patients were categorized as having no local infection, soft tissue infection or osteomyelitis treated without antibiotics, amoxicillin/clavulanacid for 1 month or ciprofloxacin and clindamycin for 3 months, respectively. Clinical outcome was assessed at 2, 6 and 12 months. Study endpoints were major amputation and mortality. Analyses were performed using the Kaplan-Meier method.*
Results. *Forty-seven of 67 patients had a local infection. Major amputation was lower in patients with successful revascularization as compared to patients unsuitable for or with failed (without) revascularization (0% vs 26%, $p < 0.01$). In patients with successful revascularization the probability of complete healing was lower with secondary infection (23% vs 71%, $p = 0.03$). In patients without revascularization complete healing was rare (<10%), but secondary infection did not influenced major amputation, mortality or serious adverse events.*
Conclusion. *Secondary infection reduces the likelihood of successful healing following revascularisation of CLI.*

Keywords: Antibiotics; Risk factors; Bypass surgery; Angioplasty; Mortality.

Introduction

Peripheral arterial disease (PAD) is a frequent cause of morbidity in industrialized countries. The annual incidence of PAD is 5–11 cases per 1000 subjects per year in people over 40 years old.[1] Twenty percentage of subjects aged over 75 years have PAD,[2] with 1–2% of them developing critical leg ischemia (CLI) within one year of follow up.[3,4] CLI is defined as chronic ischemic rest pain, ulcers, or gangrene attributed to severe arterial occlusive disease.[5] The majority of these patients have ankle pressure below 50 mmHg and toe pressure below 30 mmHg and require amputation in the absence of successful revascularization. The outcome of infections complicating critically ischemic lesions is poorly investigated. In a retrospective study reported by Kummer *et al.*,[6] secondary infection of ischemic lesions was frequent (56%), and associated with a significantly higher rate of all amputations.

This prospective single center observational study was initiated to test the hypothesis that outcome of patients with CLI and secondary infection is similar to that of patients with CLI without infection. We postulated that secondary infection treated with antibiotics is not associated with serious adverse events or mortality.

Materials and Methods

Patient selection

Three hundred and fifty patients with CLI were seen in our tertiary vascular referral centre between March 2000 and October 2003. To be included in the study, patients needed to have CLI in combination with at least one ischemic lesion present for more than 2

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weeks; A life expectancy not limited by severe cardiac failure or malignancy; A decision not to carry out primary amputation at study entry. CLI was defined according to the Second European Consensus Document.[5] Overall 67 patients with CLI and ischemic lesions qualified and agreed to participate in this prospective 12-month observational study. Patients were excluded from study participation due to the predefined exclusion criteria (33.2%, $n = 94$), unwillingness to participate (57.9%, $n = 164$), non-compliance (6.7%, $n = 19$), and failure to attend for follow up (2.1%, $n = 6$). The demographic data of participants is shown in Table 1. The study protocol was approved by the local institutional review board. All patients gave written informed consent.

Study design

In this prospective observational study consecutive patients with CLI were separated into a control group and an infection group. Infection of an ischemic lesion was suspected if two or more of the following criteria were present: peripheral body temperature >37.5 °C; ischemic lesion characterized by redness, swelling and pain; strong or putrid secretion; C−reactive protein (CRP) >5 g/l or leucocytes >10.000/μl; positive probe to bone test (infection score). Ischemic lesions with signs and symptoms of secondary infection were evaluated using conventional X-ray and magnetic resonance imaging (MRI) to determine the presence of osteomyelitis.

A standardized, empiric antibiotics regime was prescribed to all patients in the infection group. Patients with soft tissue infection were treated with amoxicillin/clavulonacid 1 g twice a day orally for 4 weeks. Patients with osteomyelitis verified by X-ray or MRI were treated with ciprofloxacin 750 mg twice daily and clindamycin 300 mg three times daily orally for 12 weeks (Fig. 1). All patients were evaluated by a team of interventionalists and vascular surgeons for optimal revascularization therapy on a case-by-case basis. Decisions were based on urgency of clinical presentation, presence of co-morbidities and arterial anatomy. In cases of prohibitive lesion pattern, patient's refusal, or if the overall clinical situation suggested an expectant attitude, CLI was treated conservatively including analgesic, antiplatelet/antithrombotic therapy and infrequently prostaglandins.

Follow up

Clinical outcome was assessed at 2, 6 and 12 month follow up. At each visit the ankle brachial index (ABI), transcutaneous partial oxygen pressure (tcpO2) measurement, and a photo documentation of the lesions were performed. Patients were evaluated for healing of lesions, minor or major amputations, adverse events, and infectious complications. Endocarditis, septicaemia and multiorgan failure were defined as serious adverse events associated with infection. Blood samples for CRP and leucocytes were collected at 2 and 12 months. Complete healing was defined as continuous viable, epithelial covering of all lesions. Successful revascularization was defined as an increase of ABI >0.1 documented for at least 30 days.[7] Amputation above the ankle was defined as major amputation. Minor amputation was defined as preservation of at least part of the foot, without requirement for prosthesis. Technical inability, missing autologous veins, high operation risk or disagreement of the patient to undergo revascularization were reported as *unsuitable* for revascularization. Documented reocclusion or failure to achieve ABI >0.1 were considered to represent *failed* revascularization. Failed and unsuitable for revascularization were summarized as *without* revascularization. Major amputation and mortality were defined as study endpoints.

Statistical analysis

Continuous data are given as mean +/− standard deviation. For observation periods the median is also noted. Odds ratio (OR) with the appropriate 95% confidence intervals (95% CI) were calculated to

Table 1. Demographic data of patients (n = 67) enrolled

	Control group ($n = 20$)			Infection group ($n = 47$)			p-value
	N	(%)		N	(%)		
Age (mean ± SD), y			74.8 ± 8.0			74.3 ± 12.9	NS
Creatinine (mean ± SD), μmol/l			105 ± 41 1 dialysis			108 ± 34 3 dialysis	NS
Men	12	(60)		31	(66)		NS
Hypertension	16	(80)		33	(70)		NS
Dyslipidaemia	8	(40)		18	(38)		NS
Obesity (BMI > 25)	13	(65)		27	(57)		NS
Smoking	11	(55)		28	(60)		NS
Diabetes	10	(50)		26	(55)		NS

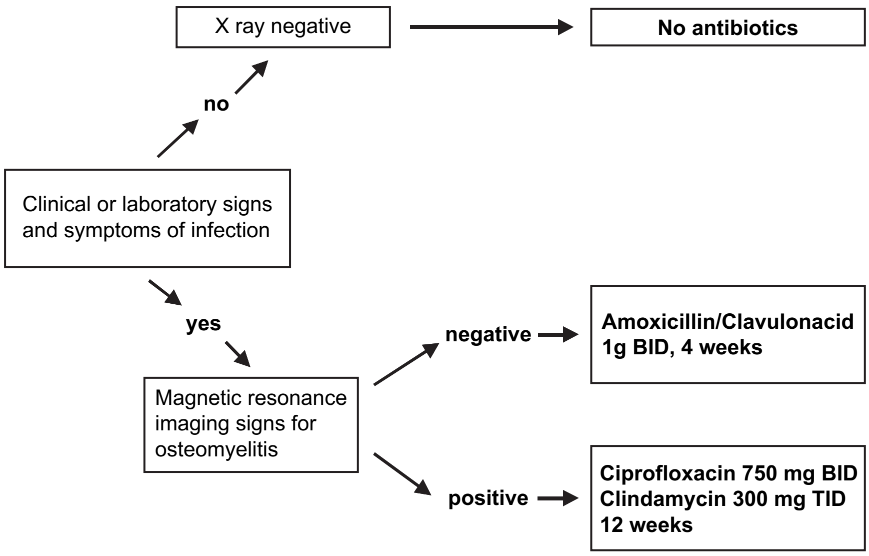

Fig. 1. Standardized antibiotic treatment according to classification of patients.

assess the relation between individual cardiovascular risk factors and major amputation. Cumulative mortality and major amputation rates were calculated using the Kaplan—Meier method. Statistical analysis was performed using Stat View software (version 4.57;SAS,Cary, ND, USA) as well as Cochrane Group software (OR). Differences achieving a p-value <0.05 were considered statistically significant.

Results

Mean follow up time for all patients was 331 (range 4 to 409) days. There was no statistically significant difference in demographic findings between control and infection groups. Forty-seven of 67 patients were classified as having secondary local infection (70%), and were enrolled in the infection group. Osteomyelitis was confirmed in 26 of 47 patients in the infection group (55%). All patients finished the intended, predefined antibiotic treatment if enrolled in the infection group. Twenty patients (30%) without signs of local infection were assigned as control group.

In a univariate analysis there was no statistically significant relation between major amputation and cardiovascular risk factors present (Fig. 2). Diabetes mellitus, renal failure, obesity and hypercholesterolemia did not influence major amputation rate. Out of 67 patients enrolled, there were 49 patients with revascularization (Table 2). Sustained clinical and hemodynamic success was achieved in 29 patients. In 18 (27%) patients neither catheter-based nor surgical revascularization could be accomplished. Successful revascularization had a significant influence on healing of ischemic lesions (10/29 vs 2/38; $p < 0.01$), and on the rate of major amputations (0/29 vs 10/38; $p < 0.01$). The presence of an infection was significantly associated with a lower probability of complete healing as compared to those lesions without signs and symptoms of infection (5/22 vs 5/7, $p = 0.03$; Table 3). Local wound management differed, in that patients with

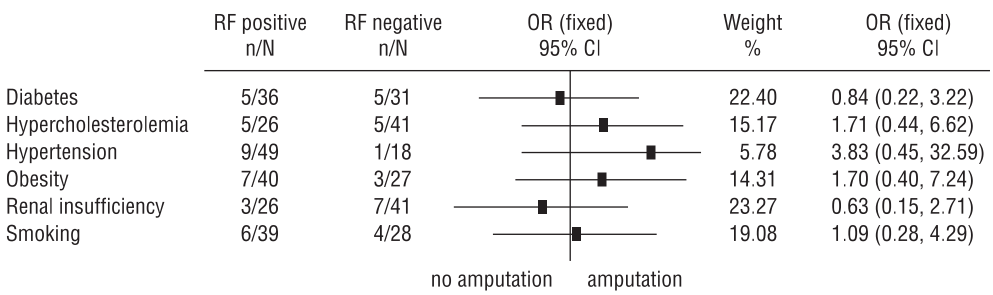

Fig. 2. Fixed odds ratios (OR) and 95% confidence intervals (95%CI) of cardiovascular risk factors present and major amputations within 12-months follow up. n/N number of events/number of participants per group; RF risk factor.

Table 2. Revascularization procedures performed within 1 years of follow up (49 patients)

Revascularization*	All ($n = 49$)	Infection ($n = 35$)	Control ($n = 14$)
Single surgical intervention	17 (25.4%)	9 (19.1%)	8 (40.0%)
Multiple surgical interventions	1 (1.5%)	0 (0%)	1 (5.0%)
Single catheter-based intervention	17 (25.4%)	16 (34.0%)	1 (5.0%)
Multiple catheter-based interventions	9 (13.4%)	8 (17.0%)	1 (5.0%)
Combination of surgical and catheter-based interventions	5 (7.5%)	2 (4.3%)	3 (15.0%)

* Several per patient possible.

successful revascularization got surgical debridement if needed and wet wound bandages, whereas lesions in patients without or with failed revascularization were decontaminated using antiseptic iodide tincture and were kept as dry as possibly to allow demarcation. In patients without revascularization, secondary infection did not influence major amputation, mortality or serious adverse events (Table 3, Fig. 3). None of the 19 deaths was directly related to an infectious complication, but was rather a consequence of the multimorbidity and high cardiovascular risk profile of patients with CLI (Fig. 3).

Discussion

This prospective observational study emphasizes that successful revascularization significantly reduces major amputation and improves healing of ischemic lesions in patients with CLI. Secondary infection of ischemic lesions is associated with a lower probability of complete healing suggesting that minor amputation without delay is recommendable in patients with successful revascularization. Our study also suggests that cardiovascular risk factors do not significantly influence limb salvage if CLI is established. This finding suggests that the prospect of limb salvage is similarly poor in all patients with CLI independent of whether a particular risk factor is present or not.

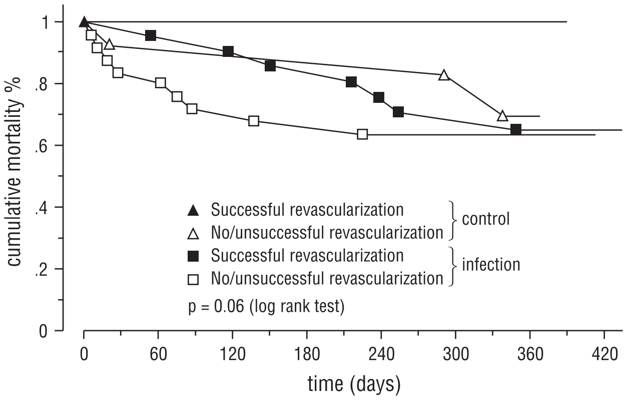

Fig. 3. Calculated cumulated survival rate of 67 patients enrolled according to revascularization status (with/without) and group assignment (control/infection).

Secondary infection of ischemic lesions in patients with CLI is not inevitably associated with major amputation or systemic complications if appropriately treated with antibiotics. Treatment of CLI should improve patient's quality of life, decrease risk of adverse events, and avoid dependence on institutional care often needed after major amputation.[8] Whether prognosis can be improved by standardized antibiotic therapy is unclear,[6] but it is known that major amputation is associated with a significant longer hospital stay, more costs, long-term institutional support and lower quality of life.[6,9–14]

Results of the present observational study support the hypothesis that secondary infection in revascularized and non-revascularized patients with CLI can be safely controlled by standardized, long-term antibiotic therapy given that optimal wound care and maximal possible revascularization is provided. Revascularisation in this series was primarily performed by endovascular means. A differing approach to wound care is needed in patients with as compared to those without revascularization. As secondary infection of ischemic lesions is associated with a lower probability of complete healing, minor amputation without delay should be considered in patients with successful

Table 3. Clinical outcome of 67 patients with CLI

	With successful revascularization*					Without revascularization & failed revascularization*				
	Infection ($n = 22$)		Control ($n = 7$)		p-value	Infection ($n = 25$)		Control ($n = 13$)		p-value
	N	(%)	N	(%)		N	(%)	N	(%)	
Complete healing	5	(22.7)	5	(71.4)	0.03	2	(8.0)	0		NS
Minor amputation	6	(27.3)	1	(14.3)	NS	2	(8.0)	1	(7.7)	NS
Major amputation	0		0		NS	5	(20.0)	5	(38.5)	NS
Persistent lesion	10	(45.5)	1	(14.3)	NS	15	(60.0)	7	(53.8)	NS
Death	7	(31.8)	0		NS	8	(32.0)	3	(23.1)	NS
Unknown	1	(4.5)	0		NS	1	(4.0)	0		NS

NS not significant;
* Several per patient possible.

revascularization to avoid long-lasting, costly wound care and immobility of the patients. Conservative, non-surgical wound care is a justified safe option in patients without revascularisation and persistence of critical ischemia. Although lesions rarely heal, there remains a chance of stabilisation and limb salvage. The non-surgical approach is supported by Treiman *et al*. who reported 91 cases with ischemic heel lesions, non leading to infection related death in a study with 21 months follow-up.[6,15] A trial published by Peterson *et al*. showed that prolonged therapy with a single broad-spectrum antimicrobial agent was successful in patients with severe peripheral vascular disease. Sixty percent of lesions were free of infection within 1-year of follow-up, including patients with osteomyelitis.[6,16] A pilot study reported by Strecker *et al*. enrolled 10 patients with CLI (6 patients with osteomyelitis), intra-arterial infusion of prostaglandin E1 and antibiotics via a subcutaneous port was successful in reducing ulcer size and induced ulcer healing in 4 patients with osteomyelitis.[6,17] In a retrospective study by Lepäntalo *et al*. analyzing 95 patients with CLI unsuitable for revascularization no more than 25% of patients were alive with both legs preserved, and the rate of major amputations was 46% at 1 year of follow up.[6,18]

Our study emphasizes the poor survival of patients with a cumulative, calculated mortality of 28% at 1 year; 34% in the infection group, and 15% in the control group, respectively. Although mortality was higher in the infection group, this was not a direct consequence of infectious complications even in those patients with failed revascularization, but rather the consequence of the multi-morbidity and pronounced cardiovascular risk profile.

Several limitations of our study need to be mentioned. Antibiotic therapy was not randomized, so we cannot exclude a decision bias. Wound care was optimized for patients enrolled and gave more favourable results as compared with published series reporting higher amputation rates in CLI.[18] Patients with extended secondary infection, often considered for primary amputation, were excluded from study entry. Moreover, based on the inherent problem of low recruitment of patients with CLI there might have been a relevant selection bias in favour of low risk patients as the majority of patients were excluded or refused to participate in this prospective follow up study.

In conclusion, secondary infection of ischemic lesions in revascularized and non-revascularized patients with CLI is not inevitably associated with major amputation or mortality if appropriately treated with a standardized antibiotic treatment. Early minor amputation should be performed to avoid long-term wound care and immobility in patients with successful revascularization. Conservative non-surgical wound management is mandatory in patients without revascularization and can safely be recommended even with signs and symptoms of local infection.

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