CLINICAL STUDY

Ultrasound-Accelerated versus Standard Catheter-Directed Thrombolysis in 102 Patients with Acute and Subacute Limb Ischemia

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ABSTRACT

Purpose: To compare the safety and efficacy of ultrasound-accelerated thrombolysis (UAT) and standard catheter-directed thrombolysis (CDT) in patients with acute and subacute limb ischemia.

Materials and Methods: Medical records of all patients treated with thrombolysis for acute and subacute limb ischemia between August 2005 and January 2012 were reviewed. Coprimary (increase in ankle-brachial index, degree of lysis) and secondary endpoints (technical success, distal embolization, bleeding complications, need for additional interventions) were assessed. UAT was performed in 75 patients, and CDT was performed in 27 patients. Patients' baseline demographic and clinical parameters and procedure details, including lytic drug infusion rate ($P = .704$ and $P = .987$), total infusion time ($P = .787$ and $P = .377$), and use of adjunctive procedures ($P = .457$), did not differ significantly between the two groups.

Results: Complete lysis was achieved in 72.0% (UAT) and 63.0% (CDT) of patients ($P = .542$); hemodynamic success was achieved in 91.8% (UAT) and 92.3% (CDT) ($P = .956$). Overall major and minor bleeding complications were observed in 6.9% (UAT) and 3.9% (CDT) of patients. Major ($P = .075$) and minor ($P = .276$) bleeding independently did not differ between UAT and CDT. Major and minor bleeding combined was lower: 6.7% (UAT) versus 22.2% (CDT) ($P = .025$). Overall target vessel patency after 8.0 months (range, 1.5–20.5 mo) was 73.5%; target vessel patency for UAT was 75.9% versus 64.3% for CDT ($P = .379$). Median long-term survival was not significantly different between UAT and CDT: 3.6 years (range, 2.42–5.33 y) versus 1.8 years (range, 1.33–4.92 y) ($P = .061$).

Conclusions: Both UAT and CDT are safe and efficient treatment modalities for patients with acute and subacute limb ischemia. The observed lower risk of total bleeding for UAT versus CDT may warrant prospective comparative trials.

ABBREVIATIONS

ABI = ankle-brachial index, CDT = catheter-directed thrombolysis, CI = confidence interval, OR = odds ratio, SSDI = Social Security Death Index, UAT = ultrasound-accelerated thrombolysis

Acute limb ischemia is a common vascular emergency with an incidence of 1.5 cases per 10,000 persons per year (1). It is defined as a sudden decrease in limb perfusion threatening viability of the limb and manifests with various symptoms such as pain, paralysis, paresthesia, pulselessness, pallor, and poikilothermy (1,2), also known as the "six P's". The time of symptom onset may vary, and limb ischemia is considered acute if symptom duration is $\leq$ 14 days, subacute if symptom duration is $>$ 14 days, and chronic if symptom duration is $>$ 3 months (3). The cause is often an underlying atherosclerotic arterial disease gradually or rapidly progressing and subsequently decreasing limb perfusion. This underlying disease has to be taken into consideration to ensure long-term treatment outcomes after successful primary revascularization (1,2).

Patients presenting with acute limb ischemia often belong to a high-risk patient population mostly because of underlying generalized atherosclerotic conditions and have high complication rates and rates of death (2).

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Many patients are unfit for open surgery. Over the years, several studies have demonstrated that catheter-directed thrombolysis (CDT) is equal in revascularization and procedure-associated deaths compared with open revascularization, although a trend toward a higher likelihood of major bleeding must be acknowledged (4–6). Despite a well-established first-line endovascular treatment algorithm (3), amputation still occurs in 10%–15% of patients during hospitalization (7,8).

Because CDT has been associated with higher bleeding rates and has not prevented all amputations, attempts have been made to improve the existing technology and related outcomes. One newer technique is ultrasound-accelerated thrombolysis (UAT). UAT was initially described in in vitro models (9–12), with the goal to disrupt the thrombus via low-intensity ultrasound to facilitate drug delivery and drug efficacy (13).

Several studies have demonstrated the successful use of UAT for the treatment of acute and subacute limb ischemia (14–18). No data directly comparing UAT with CDT have been published; the purpose of the present study was to compare safety and efficacy of these methods in the real-life setting of a tertiary care center.

MATERIALS AND METHODS

Institutional review board approval was obtained, and the need for patient informed consent for inclusion in the study was waived. In accordance with the Health Insurance Portability and Accountability Act guidelines, a retrospective review of the electronic medical records system was performed.

All adult patients who underwent treatment of acute and subacute limb ischemia with UAT or CDT at a single tertiary care medical center between August 2005 and February 2012 (78 months) were included. All patients with critical limb ischemia but without signs of acute sensory loss or paralysis were deemed suitable for an endovascular first treatment approach. The choice of treatment (UAT or CDT) and the choice of lytic drug were at the discretion of the performing physician. Demographic data, medical history, baseline laboratory values, length of occlusion, duration, and symptoms before treatment were obtained. Length of occlusion was determined by a marker catheter or radiopaque tape. Procedure-related data, such as type of catheter, type of lytic drug, infusion dose, total thrombolytic dose, and infusion times, were recorded. All available clinical data including ankle-brachial index (ABI) and follow-up imaging performed no later than May 31, 2013, were reviewed for target vessel patency. The Social Security Death Index (SSDI) was used to determine mortality as of May 31, 2013.

During the period August 2005–February 2012, 102 consecutive patients underwent lysis for acute and subacute limb ischemia. UAT was performed in 75 (73.5%) patients, and routine CDT was performed in 27 patients (26.5%). Between August 2005 and 2009, 43 interventions ($<$ 10/y) were performed, and between 2009 and February 2012, 59 interventions ($>$ 20/y) were performed. Baseline characteristics are presented in Table 1. Risk factors of acute and subacute limb ischemia—atrial fibrillation ($P = .763$), mitral valve replacement ($P = .094$), peripheral arterial disease ($P = .153$), diabetes ($P = .186$), chronic kidney disease ($P = .167$), tobacco use ($P = .091$), and reported previous arterial embolic or thrombotic events ($P = .559$)—did not differ between UAT and CDT treatment group. Medications—aspirin ($P = .459$), clopidogrel ($P = .118$), low-molecular-weight heparin ($P = .391$), warfarin ($P = .132$), and statins ($P = .873$)—also did not differ between the two treatment groups.

Definitions

Severity of acute and subacute ischemia was reported according to Rutherford criteria (19). Digital subtraction angiography was performed in all patients to determine the extent and underlying cause of the occlusion. The performing physician recorded the condition of the vasculature before and after lysis. A blinded physician who was not involved in the lysis treatment performed all imaging reviews independently to determine degree of lysis in May 2013. Similar to previous reports, success of lysis was determined by degree of lysis, defined as complete lysis ($\geq$ 90%), partial lysis (10%–90%), and no lysis ($<$ 10%) (16). Hemodynamic changes were estimated by comparing the increase of the ABI after the procedure with the ABI before the procedure in percent change. An increase of the ABI $\geq$ 0.1 after the procedure and improvement in clinical status (eg, newly palpable pulses) were used to define hemodynamic success (20,21).

Primary technical success was defined by successful positioning of the thrombolysis catheter within the thrombosed vessel. After the patient was transmitted from the interventional suite to the ward, repeated occlusion was defined as the presence of occlusive thrombus within the previously treated vessel segment, documented by follow-up imaging (computed tomography angiography, color-coded duplex sonography, or angiography).

Complete follow-up was obtained if all relevant data (eg, cardiovascular events, reinterventions) were available to the investigators at 30 days, 6 months, and 12 months and based on investigations onsite. If data for 12 months were unavailable, follow-up was not defined as "complete." SSDI data report only on survival. Event-free survival was defined as the nonexistence of any combination of death, cardiovascular events, cardiovascular interventions, or reintervention of the target vessel (ie, nonpatency).