Thrombolytic Therapy in Cocaine Users with Ischemic Stroke: A Review of Current Practice

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ABSTRACT ~ Alteplase is the main pharmacological treatment available for intravenous thrombolysis in patients with acute ischemic stroke. Endovascular treatment alone or add-on to intravenous thrombolysis is a valid approach in acute ischemic stroke with cerebral large vessel disease. The most common serious adverse reaction related to alteplase is the development of spontaneous intracerebral hemorrhage and the presence of cerebral small vessel disease may increase this risk, particularly in cocaine users, even if only few data have been published on this topic. Here we reviewed in cocaine users with acute ischemic stroke the efficacy and safety of thrombolytic therapy. Psychopharmacology Bulletin. 2019;49(1):70–79.

INTRODUCTION

Increasing evidence suggests a link between cocaine use and risk of cerebrovascular manifestations, particularly in young people. In hospitalized patients, cocaine increases the mortality in subjects affected by ischemic stroke. Cocaine induces both hemorrhagic and ischemic stroke and the stroke type varied significantly according to type of cocaine formulation as well as the contaminants and between current and previous cocaine users. In fact, crack-use is associated with both ischaemic and hemorrhagic strokes while cocaine hydrochloride-use with both subcortical (Figure 1) and subarachnoid bleeding. Current cocaine-users show a higher incidence of hemorrhagic compared to...
previous cocaine-users (37.7% v 8.6%). Multiple mechanisms may be involved in the genesis of ischemic stroke in cocaine users. Cocaine inhibits the reuptake of norepinephrine (primarily), 5-hydroxytryptamine, dopamine (resulting in a potentiation of sympathetic activity more responsible of a vasoconstriction effect) and blocks both sodium and potassium channels. Moreover, cocaine is also able to induce endothelial injury with an increase of prothrombotic activity (Figure 2). Through these mechanisms, cocaine induces myocardial infarction, congestive heart failure, arrhythmias, aortic dissection, renal failure and stroke. Chronic use of cocaine induces psychomotor effects that can responsible of mimic stroke symptoms. The use of diffusion-weighted magnetic resonance imaging (DWI-MRI) could help the differential diagnosis between ischemic stroke and mimic stroke. Here we reviewed in cocaine users with ischemic stroke the efficacy and safety of thrombolytic therapy.

**Methods**

PubMed, Embase, Cochrane library and reference lists were searched for articles published until September 5, 2018 using the keywords:
Acute Ischemic Stroke and Thrombolytic Therapy

Acute ischemic stroke causes an irreversible injury in ischemic core, and a reversible injury in the region of peri-infarct lesions (named ischemic penumbra) if a thrombolytic drug is quickly administered, within 4.5 h after the onset of symptoms and with positive score to the National Institutes of Health Stroke Scale (NIHSS). This scale is an impairment scale that may be administered quickly by physicians to evaluate the stroke severity before and after each treatment, even if is only poorly representative of the clinical deficit in posterior circulation stroke.

The ischemic penumbra consists of stratified layers, such as the selective cell death zone (heat shock protein 70-inducible zone, hypoxia inducible factor zone, and spreading depression zone) able to induce the secretion of several molecules (vascular endothelial growth...
factor, iNOS, and erythropoietin, tissue plasminogen activator).\textsuperscript{17} Although these molecules promote vascular remodeling, increase blood flow ad dissolve fibrin-based clots in the ischemic penumbra,\textsuperscript{18} these also have a destructive effect on extracellular matrix and endothelial basal lamina leading to both blood brain barrier dysfunction and hemorrhage.\textsuperscript{19}

To date the only thrombolytic drug approved to treat acute ischemic stroke is the tissue plasminogen activator (r-tPA; alteplase),\textsuperscript{20} and the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) showed that, in acute ischemic stroke, the use of recombinant tissue plasminogen activator (r-tPA; alteplase) compared with placebo increases the tissue reperfusion and reduces the growth of infarct size,\textsuperscript{21} even if its use is related to the development of bleeding\textsuperscript{22–24} and intracerebral hemorrhage (ICH).\textsuperscript{25} Therefore due to this very narrow therapeutic time window patients eligible for alteplase treatment are still between 3.4% and 5.2% of all patients with acute ischemic stroke.

Endovascular therapy, involving minimally invasive techniques for intra-arterial thrombolysis or mechanical thrombectomy, has been explored as an alternative or adjunct to medical management of acute ischemic stroke\textsuperscript{26–28} when a complete recanalization was not obtained with the intravenous treatment alone.\textsuperscript{27,29,30} Endovascular approaches offer higher recanalization rates compared with intravenous approach and has become a promising alternative for patients ineligible to intravenous thrombolysis or who failed the recanalization, particularly in presence of a basilar artery occlusion. However, mechanical approaches are associated with greater technical difficulty, excessive trauma to the vasculature potentially leading to vasospasm, vessel dissection, perforation or rupture, and fragmented thrombus causing distal embolization into previously unaffected territories.\textsuperscript{29} The endovascular treatment has other disadvantages respect to the intravenous one, i.e. a longer time to start the treatment, requires a specialized stroke centers and a network between stroke centers.\textsuperscript{29,31} Moreover, mechanical thrombectomy can’t be used in presence of microvascular stroke, but only in presence of large vessel cerebral artery.\textsuperscript{26–28,32} By the contrary, this technique offers theoretical advantages as add-on to intravenous thrombolysis compared with medical care alone, such as an increased rate and speed of recanalization and lower risk of ICH.\textsuperscript{32–34} Moreover, in presence of mismatch between deficit and infarct volume by perfusion imaging the endovascular thrombectomy is performed from 6 to 24 hours after stroke.\textsuperscript{35–38}

Vidale and Agostoni,\textsuperscript{39} analyzing 1845 patients enrolled in randomized controlled trials from 2010 to October 2016, documented that mechanical thrombectomy increases the effects of intravenous
Thrombolysis in patients with acute ischemic stroke related to arterial occlusion of proximal anterior circulation, without the development of serious adverse events. A meta-analysis demonstrated better functional outcomes and a non-inferiority mortality and ICH in patients treated with endovascular treatment compared to those treated with medical management and affected by acute ischemic stroke related to an obstruction of large-vessel anterior-circulation. Coutinho et al in a prospective clinical trial included 291 patients reported no difference in term of successful reperfusion, functional independence at 90 days, mortality at 90 days, and emboli to new territory such as symptomatic intracranial hemorrhage between patients treated with combined intravenous thrombolysis plus thrombectomy respect to patients treated with thrombectomy alone. Recently, Al-Khaled et al documented in 236 patients with stroke that rt-PA don’t increase the effect of endovascular treatment on recanalization but can improve the effect on functional outcome.

Hemorrhagic Transformation

Hemorrhagic transformation (HT), is a spontaneous complication particularly after the treatment with thrombolytic drugs. The incidence of spontaneous HT ranges from 38% to 71% in autopsy studies and from 13% to 43% in Computer Tomography studies, whereas the incidence of symptomatic HT is 0.6–20%. However, the risk of HT during alteplase treatment increases (about 10-fold higher), in patients with risk factors as age, gender, blood glucose level, blood pressure level, high National Institutes of Health Stroke Scale (NIHSS) score, severity of stroke, status of collateral vessels, time window allowed for the start of the treatment, use of double antiplatelet treatment. The presence of cerebral small vessel disease increases the risk of HT during thrombolysis in not cocaine users, it does not represent an absolute exclusion criterion to the treatment because it has a clinical benefit in these patients. Griebe et al analyzing the clinical course and the magnetic resonance imaging findings of patients treated or not with alteplase, reported that this drug is safety and efficacy in patients with small vessel cerebral artery disease. Recently, been suggested that some compounds are able to reduce the development of ICH after alteplase treatment and Reimann et al documented, in a mice experimental stroke model, that the addition of Revacept, a glycoprotein VI-Fc fusion protein, to low dose alteplase (0.35 mg/kg instead of 1 mg/kg) improves the efficacy of the treatment without the development of ICH.
**Thrombolytic Therapy in Cocaine User**

Cocaine has multiple neurovascular effects and through its mechanism of action it increases the blood pressure with the development of ICH during alteplase treatment. In fact, in cocaine-users with acute coronary syndromes, the treatment with thrombolytic drugs induces ICH.51,52

A clinical study, evaluating 3,241 stroke patients admitted to their stroke service from 2004 to 2007, documented that 132 patients were positive to cocaine metabolites and of those, 45 have ICH. In this study, cocaine-positive patients, showed higher blood pressure, severe ICH and have a 3 fold higher probability of dying during the hospitalization, respect to cocaine-negative patients.53 The same authors,53 evaluating 108 patients (mean age 48-years-old) with acute ischemic stroke treated with alteplase, did not record any difference in the development of HT, ICH or mortality between cocaine-users (n. 29; NIHSS 13) and cocaine-non users (n. 11; NIHSS score 11) (Table 1). In agreement, has been documented that the administration of alteplase to three cocaine users with human immunodeficiency virus (HIV) infection don’t induce the development of hemorrhagic transformation.54

Baud et al55 reported the development of HT after intravenous alteplase infusion in two cocaine users, 55 and 68 year-old, thrombolyzed 20 and 45 minutes after the onset of symptoms, respectively (Table 1). Both patients presented with bilateral white matter hypointensities on brain computed tomography suggestive of cerebral small vessel disease but they did not have other risk factors, such as hypertension or glucose blood level. However, prospective clinical trials are necessary to confirm these observations, and to better determine whether intravenous alteplase, in cocaine users with cerebral small vessel disease increases the risk of ICH.

In order to reduce the risk of brain bleeding, in cocaine-users, acute ischemic stroke may be treated with endovascular procedure56 and Vallee et al57 described successful thromboaspiration in a 25-year-old patient with an occlusion of the basilar artery induced by cocaine and ecstasy-use (Table 1). Similarly, MacEwen et al58 reported a 40-year-old man

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<td>Thrombolytic Therapy in Cocaine Users</td>
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<td>THROMBOLYTIC THERAPY</td>
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cocaine-user and smoker, that 11 hours after the onset of symptoms related to basilar artery occlusion (Glasgow Coma Score of 8), was successfully treated with both mechanical aspiration and intra-arterial thrombolysis (at discharge he regained four-fifths the strength in his left limbs, such that he could walk with assistance, and had only a mild scanning dysarthria). Vidale et al. reported the clinical efficacy of intra-arterial thrombolysis and aspiration (NIHSS score from 19 to 7) in a 39-year-old cocaine-user with middle cerebral artery thrombosis without hemorrhagic conversion.

**Limitations**

To date very low published papers studied the effects of alteplase in cocaine-user and some of these papers are obtained from little clinical studies and/or case reports. Therefore, further data obtained from clinical trials in larger numbers of cocaine-users are necessary to evaluate the efficacy and the safety of thrombolytic therapy.

**CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH**

Drug abuse increases the risk of stroke of 6.5-fold (95% CI 3.1 to 13.6) in all age groups and with a relative risk of 11.2 (95% CI 3.2 to 42.5) in people <35 years of age. To date alteplase represents the pharmacological treatment available for patients with ischemic stroke even if it increases the risk of intracranial bleeding. Chronic cocaine-use represents a risk factor for intracranial bleeding especially in presence of bilateral white matter hypo-intensities on brain computed tomography suggestive of cerebral small vessel disease even if to date there are only isolated reports. The increased development of HT during alteplase treatment in cocaine-user may be related to the pharmacodynamic effects of cocaine (i.e. inhibition of norepinephrine reuptake by sympathetic neurons, inhibition of 5-hydroxytryptamine and dopamine reuptake, resulting in a potentiation of sympathetic activity) rather than a vasculopathy other authors suggested also that cocaine may induce a blood-brain barrier endothelial dysfunction during alteplase treatment with an increase in ICH. Therefore, we strongly suggest to ask about cocaine exposure as part of a routine cardiovascular history or, alternatively, to perform a toxicological drug screen test in young patients with acute stroke before to start the treatment with alteplase. In chronic cocaine users, in presence of cerebral small vessel disease, the intravenous treatment may represent a risk factor of ICH and intra-arterial thrombolysis should be considered as a therapeutic option. To date, there are only anecdotal evidences...
to support these approaches, but the growing awareness of the role of cocaine in ischemic stroke should generate a sufficient number of cases to enable assessment of this treatment’s efficacy.

Further studies are needed to more definitively determine the safety and efficacy of intravenous alteplase in chronic cocaine-users with acute ischemic stroke and/or with cerebral small vessel diseases. Moreover, prospective clinical trials are necessary to demonstrate the efficacy and safety of alteplase treatment compared to endovascular treatment in these patients.

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REFERENCES