Endovascular sono-lysis using EKOS system in acute stroke patients with a main cerebral artery occlusion — A pilot study

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KEYWORDS
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Summary
Aim: Sono-lysis is a new therapeutic procedure for arterial recanalization. The aim of the study was to confirm the safety and efficacy of intravascular sono-lysis using EKOS system with 3F microcatheter EkoSonic and 2.05–2.35 MHz ultrasound frequencies.

Methods: Nine patients admitted to the stroke unit with acute middle cerebral artery (MCA) or basilar artery (BA) occlusion were enrolled to the study. Treatment using EKOS system started within 8 h after stroke onset. Neurological deficit on admission (using NIHSS), after 24 h and after 7 days, MCA/BA recanalization at the end of intervention, occurrence of symptomatic intracerebral hemorrhage (SICH), and 3-month clinical outcome (using Modified Rankin score — mRS) were evaluated.

Results: Nine patients were included in the pilot study (6 males, 3 females; age 51–80, mean 65 ± 10.4 years) with NIHSS 10–33 (median 19.0) points on admission. Five patients suffered from MCA occlusion, 4 patients from BA occlusion. Complete/partial recanalization at the end of EKOS treatment was achieved in 3 (33%)/4 (44%) patients, resp. Median NIHSS values at the end of EKOS treatment/24 h/7 days after stroke onset were 17.0/12.0/6.0 points, resp. No SICH was detected on control computed tomography. Four (44%) patients were independent at 3 months (mRS 0–3); median mRS was 4.

Conclusions: According to the results of the presented pilot study, EKOS system seems to be a new treatment option for acute stroke patients.

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Introduction

Stroke is one of the most frequent causes of mortality, morbidity and disability of population in developed countries [1,2]. Ischemic stroke (IS) is the most common type of stroke which constitutes about 80% of all strokes.

The most often cause of IS is an acute occlusion of cerebral arteries which can be demonstrated in more than 70% of patients in the first 3–6 h after onset of symptoms [3]. Very high mortality during the first month, which ranges between 10% and 17% and even up to 75% in patients with expansive ischemia, documents the importance of IS [4]. Finally, only about 30% of IS patients are independent after 3 months [2].

The independent prognostic factors of IS are not only comorbidities and complications but especially location of cerebral artery occlusion and time to recanalization. Early recanalization [within 6 h after onset of symptoms] is associated with a significantly higher chance of self-sufficiency after 90 days with a significant reduction of mortality [5]. In the last decade, the number of methods using to acceleration of artery recanalization strongly increased. In addition to pharmacological methods, especially intravenous (IVT) and intra-arterial thrombolysis (IAT) [6–8], mechanical (percutaneous transluminal angioplasty with stenting, Merci Retriever®, Penumbra®, Solitaire® stent, sono-lysis, EKOS®, EPAR®, LATIS®, Amplatz Goose-Neck Snare®, Attractor-18® or Neuronet® were tested and introduced into clinical practice similarly as in the treatment of heart ischemic syndromes [9–13].

Data from the meta-analysis of 53 clinical trials (including 2066 patients) suggests that early recanalization is present only in 24.1% patients without specific treatment (spontaneous recanalization), 46.2% patients treated with IVT, 63.2% patients treated with IAT, 67.5% of patients treated with combined IVT–IAT and in up to 83.6% patients treated with mechanical methods [5]. Nevertheless, the use of these methods only in specialized centers represents the main limitation.

Sono-lysis is one of the methods used for the acceleration of recanalization of the occluded intracranial artery.

Mechanisms of the effects of sono-lysis

Although the complex effect of ultrasound on the acceleration of thrombus lysis is not yet fully understood, it is assumed that the ultrasonic waves accelerate enzymatic fibrinolysis by primarily non-thermal mechanisms — increasing the transport of fibrinolytic agents into the thrombus by mechanical disruption of its structure [14], direct activation of fibrinolytic enzymes, either mechanical breaking of the complex molecules, in which fibrinolytic enzymes are inactivated by binding to their inhibitors, or irritation of the endothelium with increased production of fibrinolytic enzymes [15,16], transient peripheral (capillary) vasodilatation caused probably by increased production of nitrite oxide in the endothelium [17,18]. Radiation force and acoustic cavitation are the next possible and discussed mechanical effects of ultrasound [19].

In vitro and in vivo studies

Differential frequencies (20 kHz to 3.4 MHz) and intensities of ultrasound with different effects have been used in various in vitro studies [20,21]. Low frequency (about 20 kHz) and high intensity ultrasound lead to a rapid and efficient lysis of thrombi into microscopic fragments primarily by direct mechanical effect although the signs of activation of fibrinolytic lysis were also observed. These studies even demonstrated the ability of ultrasound to disrupt both fibrous and calcified atherosclerotic plaques [15,22–26]. Unfortunately thermal impairment and perforation of vascular walls were observed as side effects.

Unlike low-frequency ultrasonic waves, the high frequency ultrasound (0.5–3.4 MHz) with ultrasound intensities higher than 1 W/cm² led primarily to the increase of fibrinolytic-induced fibrinolysis [27–32]. Sono-lysis in these studies accelerated lysis of thrombus in the presence of a fibrinolytic. Without the presence of fibrinolytics, neither lysis nor mechanical thrombus fragmentation were observed.

Similar results were found also in in vivo studies with animal models [25,26,33,34]. Sono-lysis using ultrasound with low frequencies and high intensities in dog models of femoral and coronary artery resulted to recanalization of thrombosis without the use of fibrinolytic agents. However, histological signs of damage to the vascular wall were found in some models. Sono-lysis effect was demonstrated in studies in combination with a systemic administration of thrombolytics (recombinant tissue plasminogen activator — rt-PA, urokinase, streptokinase) [35,36]. Ishibashi et al. [37] studied the effect of high-frequency ultrasound with a frequency of 490 kHz and low-intensity (0.13 W/cm²) in a rabbit femoral thrombosis model to test the combined application of ultrasound-lysis with monteplase. Percentage of recanalization in combination therapy has increased from 16.7 to 66.7%.

Clinical studies in patients with acute IS

CLOTBUST trial (Combined Lysis of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic TPA) was the first randomized study testing the therapeutic effect of ultrasound (sono-lysis) in patients with acute IS [38]. In this study, all patients with acute MCA occlusion were treated with IVT. Patients were randomized to the sono-lysis group with additional therapeutic transcranial Doppler insonation with 2 MHz probe for 2 h, and control group. In sono-lysis group, there was a threefold higher chance for a complete recanalization of the occluded arteries than in the control (rt-PA only) group without the increase of the risk of symptomatic intracerebral hemorrhage (SICH). Similar results were published by Eggers et al. [39], who used sono-lysis (transcranial duplex probe with a frequency of 1.8–4 MHz) in IVT treated patients. A higher rate of complete recanalization and better early outcome and clinical status after 3 months (mRS 0–1: 21% vs. 0%) were achieved in the treatment group than in control group. However, a higher incidence of SICH (15.7% vs. 5.6%) in patients receiving sono-lysis was observed. In a multicenter case—control Thrombrotipsy study, the sono-lysis in patients with acute MCA occlusion was performed using transcranial
Endovascular sono-lysis using EKOS system

2 MHz duplex probe [40]. Length of insonation was maximum of 45 min. Percentage of arterial recanalization was significantly higher in the sono-lysis group compared to the control group (69% vs. 8% at 6 h after onset of symptoms), as well as a good clinical outcome after 90 days (mRS 0–2: 61.5% vs. 32.7%). Sono-lysis effect was more evident in the group of patients contraindicated to IVT than in IVT treated patients. Percentage of SICH was similar in the treated and control groups (3.8%).

The effect of sono-lysis in IS patients contraindicated to IVT was also described by other authors [41,42]. Eggers et al. [41] published a set of patients with acute IS and MCA occlusion treated with sono-lysis using 2 MHz duplex transcranial probe. They detected higher number of at least partial arterial recanalization and National Institutes of Health Stroke Scale (NIHSS) improvement of more than 4 points in the treated group.

In the next study, patients with acute MCA occlusion were randomized into three treatment groups — 20 patients were treated with IVT within 3 h since stroke onset, 10 patients received IAT and 10 patients were treated by 60-min sono-lysis using 2 MHz transcranial duplex probe in the 6-h time window. The study demonstrated superior efficacy and safety of sono-lysis when compared to the IVT [43]. During the first 24 h, a clinical improvement was observed in only 45% of patients treated with IVT, but in up to 70% of patients treated with sono-lysis or IAT. The incidence of SICH was 5% in the IVT group, 0% in the sono-lysis group and 20% in the IAT group.

In later sono-lysis studies, the additive effect of echocoontrast agents has been tested. The first study with Levovist® (galactose based air microbubbles, Schering, Germany) and Sonovue® (sulphurhexafluoride microbubbles, Bracco, Italy) demonstrated an increase in the percentage of arterial recanalization and better clinical improvement in acute IS patients treated with sono-lysis in combination with echocoontrast agent [44]. This study demonstrated also the safety of echocoontrast agent use. SICH occurred in 3.3% in the Levovist® group and in 2.1% in the Sonovue® group.

Better improvement of neurological symptoms as well as the improvement of the flow signal in the occluded arteries were showed in the study of Perren et al., using sono-lysis with 2 MHz transcranial duplex probe in combination with Sonovue® in patients with acute MCA occlusion treated with IVT [45].

The pilot randomized clinical trial with the new generation echocoontrast agent (perfluten-lipid microspheres) demonstrated additive effect of echocoontrast agent in patients treated with IVT and sono-lysis [46]. Percentage of complete recanalization within 2 h after therapy start was 50% in the group treated with a combination of IVT, sono-lysis and echocoontrast agent in comparison with 18% in the control group selected from the CLOTBUST study. Asymptomatic intracerebral hemorrhage was found in 25% of patients in the treatment group and in 33% in the control group. A higher percentage of asymptomatic hemorrhagic transformation was also associated with a higher percentage of recanalization and better clinical status outcome in this study. No SICH was detected. Similar results with higher recanalization rate, higher percentage of good clinical outcome and also higher number of asymptomatic hemorrhagic transformation were found by Dinia et al., who used the combination of IVT, sono-lysis and administration of echocontrast agent [47]. This result supported the hypothesis that the finding of asymptomatic hemorrhagic transformation of ischemic lesion is a marker of early reperfusion and it is associated with a higher chance of good clinical outcome.

These promising results were tested in the TUCSON (Transcranial Ultrasound in Clinical Sonothrombolysis) study. Sono-lysis using 2 MHz transcranial Doppler probe in combination with an echocontrast agent MRX-801 (perfluten-lipid microspheres, ImaRx Therapeutics, Inc., USA) as adjunctive therapy to IVT was used [48]. Although the study showed that administration of a dose of 1.4 ml of MRX-801® in 90-min continuous infusion during the IVT combined with sono-lysis is safe, the study was discontinued due to the higher SICH risk in higher dose of echocontrast agent.

Explanation of the effect of sono-lysis in the humans required several studies. The authors demonstrated a direct effect of sono-lysis on the fibrinolytic system in both healthy volunteers and IS patients using transcranial 2 MHz duplex probe [15,16,49]. In healthy volunteers, 1-h sono-lysis of MCA or radial artery led to the decrease of fibrinolysis inhibitors (PAI-1 antigen, plasminogen activity and alpha-2 antiplasmin) levels [16,49]. Similar results were obtained in patients with acute IS. Also t-PA antigen was increased in sono-lysis group in comparison with a control group. These findings were more evident in patients treated with IVT in combination with sono-lysis than in sono-lysis group only. There were no significant differences in the number of SICH between the groups. This study demonstrated that acti- vation of the fibrinolytic system is one of the therapeutic effects of ultrasound.

On the contrary to the studies with diagnostic frequencies, studies with lower frequency (300 kHz) ultrasound led to the increased risk of intracranial bleeding and blood–brain barrier breakdown.

TRUMBI (TRanscranial low-frequency Ultrasound Mediated thrombolysis in Brain Ischemia) study used low-frequency ultrasound (300 kHz, the intensity of 700 mW/cm²) for 90 min for sono-lysis in patients with acute cerebral artery occlusion treated with IVT. The study was early terminated due to the extreme increase in the risk of SICH and of subarachnoid hemorrhage [50]. One of the hypotheses explains the increased risk of bleeding in the study by the abnormal permeability of the blood–brain barrier in humans caused by low frequency ultrasound. Multiple reflecting and focusing of ultrasonic waves within the skull, which can significantly increase the intensity of ultrasound applied in some areas of the brain, represent another option. The increased risk could also contributed to the excessive activation of the endogenous fibrinolytic system in combination with IVT.

Reinhard et al. [51] demonstrated that 60-min sono-lysis using an ultrasound frequency of 300 kHz leads to the increased permeability of the blood–brain barrier. The study was also prematurely terminated after the inclusion of 4 patients.

Clinical studies with endovascular sono-lysis

EKOS system® is the first system that allows the application of endovascular ultrasound-lysis, using a catheter
for intra-arterial administration of drugs (e.g. thrombolytics) terminated with the emitter of ultrasonic waves. It emits ultrasound waves with the frequency between 1.7 and 2.35 MHz and with the emitted intensity of 400 mW/cm² into the thrombus. The first clinical studies with endovascular sono-lysis were used for the coronary arteries. In the ACUTE (Analysis of Coronary Ultrasound Thrombolysis Endpoints in Acute Myocardial Infarction) study, the low-frequency (45 kHz) ultrasound with a high intensity (18 W/cm²) was used in acute coronary artery occlusion [52]. Complete recanalization was achieved in 87% patients. No side effects were observed during the therapy and 80% of patients showed clinical improvement.

Other studies showed the effect of endovascular ultrasound-lysis by EKOS system in patients with deep venous thrombosis of lower extremities and in patients with pulmonary embolism [53—56].

Mahon et al. [57] published the first experience with endovascular sono-lysis using the EKOS system in patients with acute IS. They used a combination of IAT using rt-PA with endovascular ultrasound applied continuously for 60 min in 10 patients with MCA occlusion and in 4 patients with BA occlusion. Partial or complete recanalization was detected in 57% patients and there were no adverse effects observed during the therapy.

The authors also performed a prospective mono-centric study aimed to confirm a safety and efficacy of intravascular sono-lysis using EKOS system® with 3F microcatheter EkoSonic and 2.05—2.35 MHz ultrasound frequencies for the recanalization of brain arteries in acute stroke patients within an 8-h time window.

Material and methods
The pilot, prospective, observational, single center study of consecutive patients presenting with acute stroke symptoms and radiologically confirmed MCA or BA occlusion was performed. The entire study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 1983, 2004 and 2008). It was approved by the Local Ethics Committee of University Hospital Ostrava. All subjects signed informed consent. In case of technical problems with regard to signing, their signature was also verified by an independent witness.

Patients with (1) acute IS, (2) NIHSS score of 10—24 points on admission, (3) MCA or BA occlusion detected by computed tomography (CT) angiography and digital subtraction angiography (DSA) (Fig. 1a and b), (4) admitted and treated within 8 h since stroke onset, and with (5) signed informed consent were consecutively enrolled to the study during 12 months.

Exclusion criteria were (1) previous disability, (2) intracranial bleeding or tumor on brain CT, (3) infarction on brain CT in more than 2/3 of the MCA territory, and (4) partial or complete recanalization of brain artery after IVT treatment detected using transcranial duplex sonography.

A physical examination, blood samples, electrocardiogram, chest X-ray, and standard neurologic evaluation by a certified neurologist using the NIHSS were performed on admission followed by brain CT and CT angiography (CTA) of cervical and intracranial arteries. Patients underwent standard treatment [58,59]. Patients who fulfilled SITS-MOST criteria [60] for IVT were treated using rt-PA intravenously (0.9 mg/kg) within 4.5 h since stroke onset. Secondary preventive therapy was administered according to the European Stroke Organisation guidelines [59].

Endovascular sono-lysis using EKOS system
The interventional procedure started with arterial puncture via femoral approach. At the beginning of the procedure, heparin was administered intraarterially (50 IU/kg). Then, the 6F sheath insertion was performed with standard Seldinger technique. All patients underwent 4-vessel diagnostic angiography with 4 or 5F pre-shaped catheters inserted over the 0.035 in. diameter hydrophilic wires. The 6F guiding catheter was introduced subsequently into the target brain supplying vessel over the same hydrophilic wire and microcatheter with a support of a 0.014 in./300 microwire was advanced behind the occluded intracranial vessel segment. Occlusion of MCA or BA was classified according to the Thrombolysis in Cerebral Ischemic (TICI)
criteria. The intraluminal position of the microcatheter was always checked. All catheters were continuously flushed with heparinized saline. The microcatheter was then replaced with the EKOS endovascular catheter terminated with the emitter of ultrasonic waves and connected to the central unit. The EndoWave System manufactured by EKOS Corporation (Bothell, WA, USA) was used (Fig. 2a and b). It consists of a 5.2F, 106 cm long infusion catheter, an ultrasound core wire, and a control unit with catheter interface cables. The ultrasound wire delivers pulsed high frequency (1.7–2.1 MHz) and low-intensity (400 mW/cm²) ultrasound waves. Special care was taken for the location of a tip of the catheter into the occluded segment of the artery (Fig. 3). Both the insonation and the local administration of tPA directly into the thrombus were simultaneously started. In this study, a dose of 15 mg/h of tPA was delivered by an infusion pump with a maximal calculated total dosage not exceeding 20 mg of tPA.

Patients with partial recanalization after EKOS treatment were further treated by angioplasty and stent implantation.

Radiological and clinical evaluation
The recanalization status at the end of DSA was evaluated by blinded independent radiologist using the TICI criteria. TICI IIc and III were evaluated as complete recanalization (Fig. 4), TICI IIa and IIb were evaluated as partial recanalization.

Neurological and physical examinations were done before therapy start and 24 h, 30 and 90 days after the start of treatment. Certified neurologist performed evaluation of neurological symptoms using NIHSS in all visits. Modified Rankin score was used for the evaluation of disability at days...
30 and 90. Good clinical outcome was defined as a mRS 0–3, poor clinical outcome as a mRS 4–6.

All adverse events were recorded. All changes in physical examinations, worsening of neurological symptoms (>4 points in NIHSS) and all disorders prolonging or requiring hospitalization were recorded as adverse events.

Intracranial bleeds detected in the control brain CT examination 24 h after therapy onset were recorded. Intracranial bleeding with worsening of neurological symptoms > 4 points in the NIHSS were evaluated as SICH (ECASS 3 criteria). Other intracranial bleeds were evaluated as asymptomatic intracranial hemorrhage (AICh).

In the control brain CT scan, detected brain edema associated with worsening of neurological symptoms > 4 points in the NIHSS was evaluated as “symptomatic”.

Statistical analysis
Data with a normal distribution was reported as mean ± standard deviation. All parameters not fitting to a normal distribution were presented as median and range. Statistical analyses were performed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA).

Results
Nine patients (6 males, 3 females) were included in the pilot study. The age range was 51–80, mean 65.0 ± 10.4 years. NIHSS on admission was 10–33 with median of 19.0 points. Five patients suffered from MCA occlusion, 4 patients form BA occlusion. Mean time onset-to-treatment was 282 ± 184 min.

Complete recanalization at the end of EKOS treatment was achieved in 3 (33%) and partial in 4 (44%) patients, resp. Mean time between diagnostic angiography and artery recanalization was 108.1 ± 39.9 min. No SICH or symptomatic brain edema were detected on control CT.

Median NIHSS at the end of EKOS treatment was 17.0 points. After 24 h, the median NIHSS was 12.0 and 7 days after stroke onset 6.0 points, resp. Four (44%) patients were independent at 3 months (mRS 0–3); median mRS was 4.

Discussion
The results of the pilot study demonstrated safety of endovascular sono-lysis using the EKOS system. SICH and also malignant infarction were not detected in any patient.

Partial or complete recanalization of brain artery was achieved in 77% patients in the presented study. In the similar study, Mahon et al. [57] achieved any recanalization only in 57% patients treated by endovascular sono-lysis using the EKOS system.

Presented results are comparable with other studies using mechanical methods for brain artery recanalization. In the MultiMerci study the partial or complete recanalization was achieved in 55% patients with 9.8% occurrence of SICH [61]. Higher recanalization rate was demonstrated in the study with Penumbra system. Partial recanalization was achieved in 54% patients and complete recanalization in 33% patients with 5.7% of periprocedural complications [62]. However, the highest recanalization rates were achieved using the Solitaire stents. In the recent studies, partial or complete recanalization of brain artery was achieved in 88–90% patients with the occurrence of SICH of 2–17% and less than 8% of periprocedural complications [63–66].

Although the recanalization rate in published studies using new devices was quite high and still increasing, the number of independent patients did not exceed 60%. 44% patients in the presented study were independent 90 days after stroke onset. In the previously mentioned studies, 31–59% patients were independent at day 90 with mRS 0–3 [61–66].

Several limitations of the presented study should be mentioned. This was a single center observational pilot study. The main goal was to assess the safety of endovascular sono-lysis. Evaluation of artery recanalization is still very subjective even though the vascular status was evaluated by blinded radiologist in the presented study.

In the future, the randomized multicenter study has to be performed to confirm a potential effect of endovascular sono-lysis on the acceleration of artery recanalization.

Conclusion
Sono-lysis is a promising method of treatment of acute IS. This is a relatively safe treatment with a high efficacy in the acceleration of cerebral arteries recanalization. A good availability and a low price are the advantages of transcranial sono-lysis, but its use is limited by the quality of the temporal bone window and the availability of an experienced sonographer. Also endovascular sono-lysis seems to be safe and effective. It is not dependent on the bone window quality, but it is limited by the availability of interventional radiologist. Further double-blind randomized studies are needed to confirm the safety and efficacy of sono-lysis, and especially to determine the optimal frequency, intensity and character of the ultrasonic waves.

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