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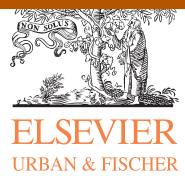

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Sonothrombolysis for treatment of acute ischemic stroke: Current evidence and new developments

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Acute ischemic stroke;
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Summary Sonothrombolysis is a novel therapy for recanalization of acute intracranial arterial occlusion. So far, safety and efficacy has been shown for transcranial ultrasound with diagnostic probes in combination with standard thrombolysis treatment. However, there are several new developments including special designed ultrasound probes, microspheres for enhancement of the thrombolytic effect of ultrasound and other new approaches. This review provides an overview of current evidence from randomized controlled trials and perspectives on this topic.

Introduction

Sonothrombolysis has been introduced for treatment of acute intracranial occlusions during the first years of the last decade. Improved recanalization has been demonstrated with ''diagnostic'' transcranial ultrasound (US) in combination with standard intravenous (IV) thrombolysis with recombinant tissue-plasminogen activator (rtPA) in two randomized trials [1,2]. A study with limited sample size on middle cerebral artery (MCA) main stem occlusion has indicated that this method might be a possible alternative to interventional therapy [2]. The occurrence of an increased rate of symptomatic hemorrhagic transformation of brain infarction after sonothrombolysis with diagnostic US has not been confirmed thus far [3]. In the absence of other therapies (e.g., in cases of contraindication to thrombolytic drugs or thrombus extraction), this method may serve as an alternative treatment, as indicated by the findings of a small randomized study using transcranial color-coded sonography (TCCS)-guided pulsed-wave (PW) US [4]. Novel developments include microspheres-enhanced thrombolysis for improved drug delivery and enhancement of microcirculation [5,6]. A recent pilot study has tested the feasibility of using an intra-arterial high-energy US catheter for recanalization [7]. Although many promising advances have been made in the field of sonothrombolysis, ''diagnostic'' transcranial US remains the only method that has been shown to be effective and safe. The aim of this review is to provide an overview of confirmed evidence and perspectives on sonothrombolysis for the treatment of acute ischemic stroke (AIS).

Clinical evidence

From random observation to therapy

The thrombolytic effect of ''diagnostic'' transcranial US in acute intracranial occlusion was discovered more than 10 years ago at 3 stroke therapy centers, independently of each other. At the Center for Noninvasive Brain Perfusion Studies at the University of Texas-Houston Medical School, physicians noticed that patients receiving continuous transcranial US monitoring for determination of rtPA-associated

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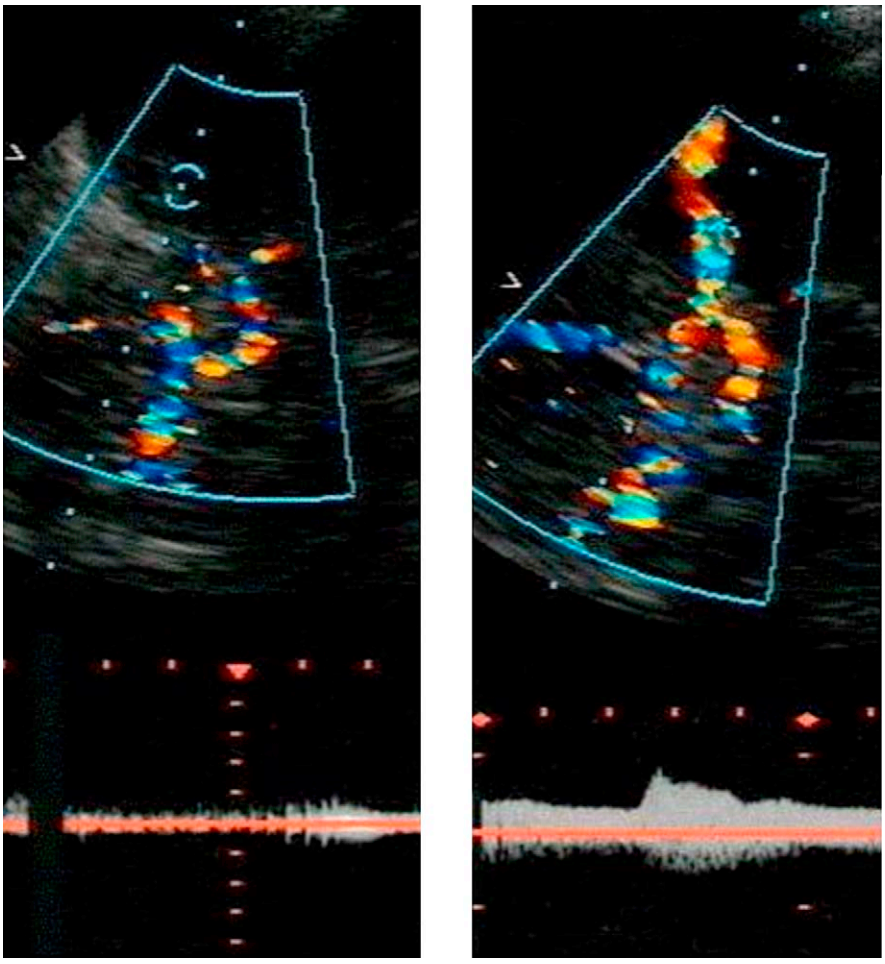

Figure 1 Transcranial image in color-coded mode of transcranial color-coded sonography (TCCS). Proximal middle cerebral artery (MCA) main stem occlusion (left) with complete recanalization at 1 h after intravenous (IV) recombinant tissue-type plasminogen activator (rtPA) plus sonothrombolysis (right).

recanalization more frequently exhibited a favorable clinical course in comparison to patients without monitoring [8]. Based on these results, a randomized, multicenter clinical trial, known as the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA (CLOTBUST) trial, was performed to study this effect. A similar effect was observed with TCCS in the stroke unit at the University of Lübeck, Germany [9] (Fig. 1). In contrast to the multicenter CLOTBUST trial, this monocenter, randomized study also included patients with contraindications to rtPA. In addition, neurologists at the University Hospital Ostrava, Czech Republic, observed a similar effect in patients with acute cerebral artery occlusion during examination with TCCS [10].

Results of randomized studies

The CLOTBUST trial included a total of 126 patients with occlusion of the main segment of the stem or branches of the MCA. All subjects were treated with standard IV rtPA and were additionally randomized for a 2-h insonation with transcranial Doppler (TCD). The primary endpoint (complete recanalization or substantial clinical improvement) was more frequently reached in the sonothrombolysis group (40%) than in the standard therapy group (30%). No significant differences were found in the clinical results obtained after 24 h and after 3 months. However, a clear tendency for functional independence after 3 months was detected in the sonothrombolysis group. The rate of symptomatic intracranial hemorrhage (sICH) was the same for each group (4.8%) [1]. Some limitations of the CLOTBUST trial were the inclusion of an inhomogeneous patient sample (MCA main stem and branch occlusions) and the definition of the primary endpoint. The US imaging of the thrombus, carried out with blind TCD sonography by means of a probe attached to the head, may also have been inadequate, particularly in branch occlusions or occlusions of the main stem without residual flow. Despite these limitations, this multicenter trial can be considered a proof of principle study.

In the Lübeck study, patients were randomly selected to receive TCCS-guided PW mode US for 1 h. The color duplex mode was used to improve the accuracy of focusing the US on the thrombus. Patients with exclusively proximal MCA main stem occlusions without residual flow who underwent simultaneously insonation and rtPA standard treatment were included in the study. The homogeneity of the sample was not only a major strength of the study but also its weakness

(i.e., only a relatively low number of patients [$n = 37$] were included in this monocenter study). Similar to the findings of the CLOTBUST trial, continuous insonation for 1 h (instead of 2 h like in the CLOTBUST trial) resulted in significantly improved recanalization (partial or complete recanalization: 58% in the continuous insonation group vs. 22% in the control group). Additionally, an improvement in neurological deficits after 4 days, and a clear trend toward better functional outcome after 3 months in patients was shown. Tendencies for increased symptomatic cerebral bleeding (3 patients in the sonothrombolysis group vs. 1 patient in the control group) and increased hemorrhagic transformation of infarcts were also found in patients who underwent continuous insonation [2]. A total of 15 patients were randomized in the arm of the trial for patients with contraindications to rtPA. Recanalization (all of them were partial recanalizations) after 1 h occurred only in the sonothrombolysis group (62.5% in the sonothrombolysis group vs. 0% in the control group). Significant improvements in clinical course after 4 days and functional independence after 3 months were found in 2 of 8 patients in the sonothrombolysis group (compared with none of the 7 patients in the control group) [4]. No sICHs occurred in the sonothrombolysis group. At the end of the randomized trial, this treatment principle was continued in the context of a clinical register. Currently available data (obtained from a total of 116 patients with MCA main stem occlusions, with or without rtPA treatment) confirm these results (unpublished data).

Sonothrombolysis with TCCS in combination with rtPA: an alternative to interventional treatment?

For occlusions of the main intracranial arteries, IV thrombolysis alone is probably not adequate to achieve early recanalization, which explains why interventional therapy, either intra-arterial thrombolysis or thrombus extraction, is often regarded as an alternative. However, in addition to the yet unsatisfactory evidence attained from randomized clinical trials for these interventional therapies, there are two important limitations: the time delay to the start of the intra-arterial intervention and the lack of availability of these types of interventional treatment in nonspecialized centers. Sonothrombolysis as a tool to improve the effectiveness of IV thrombolysis may be a promising alternative option. A comparison of the published randomized data and those from the randomized study of intra-arterial thrombolysis, known as Prolyse in Acute Cerebral Thromboembolism II (PROACT II) [11], revealed very similar recanalization rates, although more severe occlusions were treated in the sonothrombolysis study (proximal MCA-M1 occlusions in contrast to M1 and M2 branch occlusions in PROACT II). As shown in Fig. 2, rates of recanalization in the PROACT II study were quite similar to those obtained in the sonothrombolysis with TCCS and rtPA study. The PROACT II study randomized patients with MCA main stem or M2 branch occlusions within a 6-h time window for intra-arterial thrombolysis with pro-urokinase. The sonothrombolysis with TCCS and IV rtPA study randomized patients with proximal MCA main stem occlusions without residual flow (including patients with additional ipsilateral internal carotid artery occlusion) within a 3-h time window for 1 h of continuous insonation. As

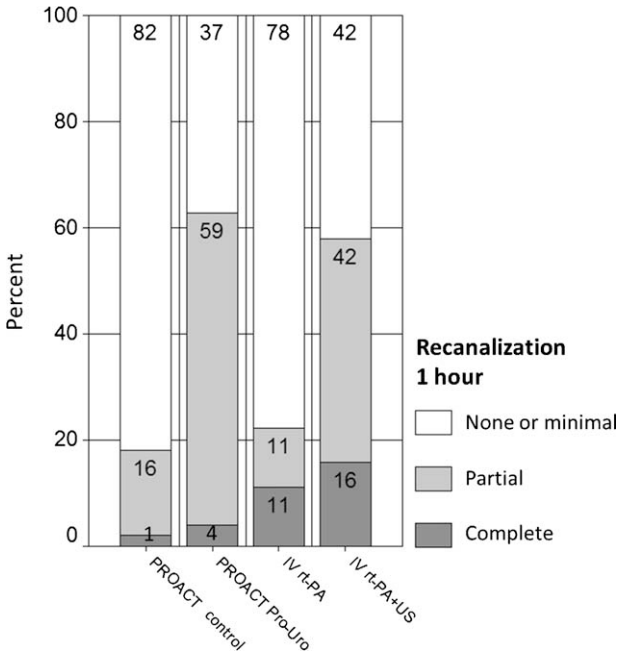

Figure 2 Recanalization rates after 1 h from the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study compared with those from the sonothrombolysis with TCCS and rtPA study. Partial/complete recanalization was defined as follows: Thrombolysis in Myocardial Infarction (TIMI) 2/3 in PROACT II, and Thrombolysis in Brain Ischemia (TIBI) Doppler score [40] 2—3/4—5 in the sonothrombolysis with TCCS and rtPA study. For the PROACT II study, 162 patients were 2:1 randomized for therapy vs. control, for the sonothrombolysis study 37 patients were randomized 1:1 for rtPA plus 1 h insonation (US) vs. rtPA alone.

shown in Fig. 3, comparable outcome results after 3 months (3—4 months in PROACT II) were obtained for the sonothrombolysis with TCCS and IV rtPA group and the pro-urokinase treatment group. The strong tendency toward a worse outcome for patients in the IV rtPA group without sonothrombolysis compared with those in the PROACT II control group may indicate that patients in the Lübeck randomized study may have been more severely affected than those in the PROACT II study.

Limitations of sonothrombolysis

The lack of a temporal bone window is one main limitation of sonothrombolysis. Research studies have revealed that the frequency of an insufficient temporal sound window for TCCS can vary from 8% [12] to 27% [13]. On the other hand, also the interventional therapy may not be applicable for all patients. A common limitation of interventional therapy is the lack of patency of the proximal carotid artery. Data from the own register of MCA-M1 occlusions have revealed the presence of an additional proximal occlusion of the internal carotid artery in 23% of patients (unpublished data).

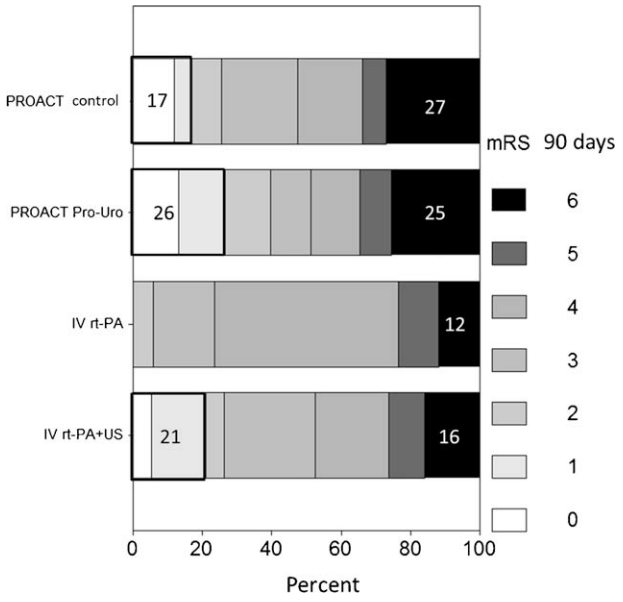

Figure 3 Functional results after 90 days (in the Prolyse in Acute Cerebral Thromboembolism II [PROACT II] collective, 90—120 days) as measured on the modified Rankin scale (mRS). Median National Institutes of Health Stroke Scale (NIHSS) scores on inclusion: PROACT II, 17 for control group and 17 for pro-urokinase group; sonothrombolysis with transcranial color-coded sonography (TCCS) and recombinant tissue-type plasminogen activator (rtPA) study, 18 for IV rtPA and 18 for IV rtPA plus ultrasound (US). The percentages in the bars give the rate of mRS scores (0—1) or the mortality at 90 days (90—120 days in PROACT II). Number of randomized patients in PROACT II, 162; in the sonothrombolysis study, 37. Rate of symptomatic intracranial hemorrhage (sICH): 10% in the pro-urokinase group, 15% in the sonothrombolysis group. Differences were not statistically significant.

Meta-analysis of clinical results of sonothrombolysis

A meta-analysis conducted by Tsivgoulis et al. [3] on sonothrombolysis with transcranial US (TCCS or TCD) included over 400 patients. They found that in comparison to patients with rtPA treatment alone, patients who underwent sonothrombolysis had a 3 times higher chance for complete recanalization and a 2 times higher chance for non-disability after 3 months. There was no evidence for increased risk of cerebral bleeding with US treatment.

From bedside to bench: experimental evidence

When the thrombolytic effect of ''diagnostic'' transcranial US was clinically observed for the first time, no experimental data on the effect of high-frequency, low-energy PW US on thrombolysis were available at the time. However, during the 1990s (after much time had passed since the first description of the thrombolytic effect of US in the late 1970s [14]), in vitro studies using high-frequency (1 MHz) and high-energy (spatial peak temporal average intensity [I_{SPTA}] of 2 W/cm^2) US demonstrated improved US-mediated binding of rtPA to fibrin, as well as reversible disintegration of fibrin without thrombolytics [15]. By contrast, in the Lübeck study, the transducers for ''diagnostic'' transcranial use employed frequencies between 1.8 and 2.5 MHz and had a I_{SPTA} of 179/cm^2, and most of the energy was absorbed by the skull. For neurological disorders, only two in vitro studies on the transcranial use of US for acceleration of thrombolysis were available at this time: These studies showed the effect of low-frequency US in combination with a thrombolytic on fibrin-rich thrombi [16,17]. However, the US used in these two studies differed substantially from the diagnostic US of a probe for TCCS: The frequencies used in the in vitro studies were in the range of 33—211 kHz, leading to good penetration of emitted US energy through the skull (e.g., by 40% in the Akiyama et al. [16] study). In comparison, up to 90% of energy from a high-frequency (1.8—2.5 MHz) ''diagnostic'' transcranial US probe was absorbed by the skull [18,19]. To obtain more information about the thrombolytic effect of ''diagnostic'' transcranial US, corresponding in vitro studies were done. In addition to the effect on the thrombolysis of whole venous blood clots, the effect on platelet-rich clots (PRCs) was investigated. The effect of US in combination with abciximab, the glycoprotein IIb/IIIa receptor inhibitor, was also examined and compared with the effect of rtPA. One main finding was that sonothrombolysis in combination with rtPA had a greater effect on whole venous blood clots and PRCs than sonothrombolysis in combination with abciximab. Because sonothrombolysis in combination with abciximab produced very disappointing results, including a weak effect on PRCs, this combination could not be recommended [20,21]. A study by Pfaffenberger et al. [19], which compared the impact of duplex-Doppler, continuous wave-Doppler, and PW-Doppler on rtPA-mediated thrombolysis, found that only the PW mode significantly accelerated rtPA-mediated thrombolysis.

Perspectives for sonothrombolysis

Operator-independent device for sonothrombolysis

A multicenter, randomized clinical trial will be launched to evaluate the safety and applicability of a novel operator-independent device for sonothrombolysis. A total of 900 patients who receive standard IV rtPA treatment will be randomized for 2-MHz PW US vs. sham treatment. The primary outcome endpoint will be functional independence after 3 months, and sICH will be assessed as the primary safety endpoint [22]. The introduction of a semi-automatic novel device for sonothrombolysis may overcome the disadvantages of conventional diagnostic US probes, which are considered time-consuming and operator intensive.

Other types of US

The results of previously conducted randomized clinical trials were based on the randomly observed effects of transcranial imaging generated by commercial diagnostic US devices. An early attempt to enhance thrombolysis by using US probes dedicated for optimized sonothrombolysis did not yield promising results. A multicenter, randomized clinical trial investigating the effectiveness of a specially

developed ''sonothrombolysis probe'' with a higher energy and lower frequency for improved penetration of the skull (Transcranial Low-frequency Ultrasound-mediated Thrombolysis in Brain Ischemia [TRUMBI] study) unfortunately resulted in a higher rate of sICH [23]. Cerebral bleeding after treatment also occurred on the opposite side of the brain infarction, suggesting a causal link to the substantially higher energy and lower frequency of the ''sonothrombolysis probe'' compared with the energy of diagnostic US probes. In vivo experiments evaluating the therapeutic efficacy and safety of using highly energetic, low-frequency (20 kHz) US in treating rats with an embolic MCA occlusion showed an increased incidence of cerebral edema [24,25], thus indicating the unsuitability of this kind of US for clinical use. So far, ''diagnostic'' transcranial US remains the only form of US appropriate for sonothrombolysis.

Endovascular sonothrombolysis: results from a pilot study

Skoloudik et al. [7] performed a pilot study on 9 patients who had suffered an AIS with acute MCA or basilar artery occlusion and undergone endovascular sonothrombolysis within an 8-h time window from symptom onset. For this purpose, a 3F microcatheter with a US probe of 2.05—2.35 MHz was used. Complete recanalization at the end of treatment was achieved in one third of patients, and partial recanalization occurred in an additional 44% of patients at the end of the procedure. At admission, the National Institutes of Health Stroke Scale (NIHSS) scores were in the range of 10—33 (median, 19.0). At 3 months, 4 (44%) patients were functionally independent (modified Rankin Scale [mRS] score, 0—3; median mRS score, 4). No sICHs occurred for 24 h after endovascular sonothrombolysis until a control computed tomography (CT) scan at 24 h. These researchers concluded that this endovascular system might serve as a new treatment option for patients suffering from acute stroke.

US can control embolus growth—can transcranial US prevent early reocclusion?

The thrombolytic effect of US has generally been regarded as a tool for improving recanalization. However, as several US follow-up studies have shown, reocclusion of a vessel after recanalization can occur in 20% or more (up to 29%) of patients after rtPA treatment [1,26]. Sawaguchi et al. [27] recently reported interesting results from a novel use of US treatment in AIS. They found that continuous US (500 kHz, 0.72—0.28 W/cm^2) significantly suppressed thrombus growth in vitro. Based on their findings, these researchers suggested low-intensity, low-energy US as a possible simple and safe tool to prevent reocclusion of intracranial vessels after rtPA treatment.

What is the most effective US for sonothrombolysis? Systemic evaluation using standardized experimental settings

Determining the most efficient US settings for sonothrombolysis is complicated by the fact that there is a tremendous number of possible combinations of its parameters. Wang et al. [28] presented results from an in vitro experiment for the systematic and rapid evaluation of the thrombolytic effect of 500-kHz US as the ultrasonic spatial intensity increased from 0.1 to 0.7 mW/cm^2. For this purpose, flat discoid clots were simultaneously made in specially designed wells with a thin polycarbonate base that is transparent to light and reflects little US. The extent of clot lysis was automatically measured by means of light absorbance at a wavelength of 412 nm using a spectrometer before and after thrombolytic treatment. This method allowed the researchers to measure automatically a total of 200 positions within minutes, representing a throughput about 100 times as large as that of conventional methods.

Magnetic resonance imaging (MRI)-guided US for sonothrombolysis

Magnetic resonance-guided focused ultrasound (MRgFUS) is a novel method for optimizing US treatment. In general, magnetic resonance imaging (MRI) enables the adjustment of the US beam, based on differences in temperature measurements in the targeted parenchyma. For the purpose of sonothrombolysis, preliminary steps have involved using in vitro models with human skull and porcine brain. In future, it may be possible to detect the thrombus within the vessel, to focus the US beam on this target, and make corrections to the US beam so as to avoid side effects of US caused by distortion and shifting of the human skull [29,30].

Microspheres for enhancement of sonothrombolysis: current state and new developments

Another way of enhancing the effect of sonothrombolysis involves the use of microspheres. Commercially manufactured ultrasonic contrast amplifiers have been used in several studies: SonoVue®, which consists of sulfur hexafluoride-filled microbubbles of phospholipids, and Levovist®, a granulate of galactose and palmitic acid, which binds to micrometer-sized air bubbles. Following IV injection, they take energy on under influence of US, and by oscillation or rupture, this energy is released again, which reinforces the US effectiveness. Various experiments have shown the effectiveness of this method without an increase in the intracranial bleeding rate, which has been demonstrated in vivo. Molina et al. [31] showed an improvement by intermittent bolus injection of Levovist® in addition to tPA treatment plus 2-h insonation with TCD monitoring. A similar study was conducted by Perren et al. [32] in which patients who had suffered from an MCA stroke underwent IV rtPA thrombolysis and 2-MHz TCCS monitoring for 1 h with SonoVue®, resulting in clinical improvement in these patients. No additional intracranial bleedings were noted in these studies. In the transcranial ultrasound in clinical sonothrombolysis (TUCSON) randomized clinical trial, intravenously applied microspheres, which had been developed for the purpose of strengthening the effect of sonothrombolysis, were clinically tested [5]. This dose-escalation study of microspheres showed increased bleeding in the second dose

tier, prompting the sponsor of the study to discontinue this approach.

Microspheres with abciximab for better thrombus binding and identification and improved sonothrombolysis

In vivo molecular imaging of the human thrombus can be carried out with microspheres conjugated with abciximab, a glycoprotein IIb/IIIa receptor inhibitor that is involved in ligand targeting of the thrombus. In vitro experiments have shown that improved binding of microspheres to the clot enhances sonothrombolysis [33,34].

Nanodroplet-enhanced sonothrombolysis

In their 2011 study, Shimizu et al. [35] reported preliminary results from an in vivo animal safety evaluation in vivo experiment with superheated perfluorocarbon nanodroplets (SPNs). When triggered by US, these nanodroplets turn into microbubbles. During this in vivo experiment, rabbits received either an IV injection of SPNs or a placebo without additional insonation. Within an hour after administration of SPNs, 4 cases showed a reversible change in respiration; 1 animal showed transient horizontal nystagmus about 20 min after administration of SPNs. Following euthanasia, no neuropathological damage or histological damage could be shown in any organ sample from any of the animals included in the study. The biochemical blood examination revealed no significant differences between the SPN-treated group and the placebo group. These researchers plan to conduct a study investigating the SPN-assisted sonothrombolytic effect of 500-kHz US exposure.

US-targeted drug delivery to the brain

In addition to enhancing sonothrombolysis, the combination of transcranial US and microspheres may have another purpose—that is, facilitating the delivery of drugs across the blood—brain barrier (BBB). Substances or drugs (e.g., large-molecule agents such as monoclonal antibodies, recombinant proteins, and gene therapeutics) that would be potentially useful for treatment of a variety of central nervous system disorders cannot penetrate the BBB. New developments have shown that noninvasive, targeted, US-induced disruption of the BBB could facilitate drug delivery. Transcranial-focused US penetrates the skull, thus preventing the need for trepanation. Targeting of the US beam can also be optimized by MRI [36—38].

Improvement of microcirculation

In addition to recanalization, microcirculation of ischemic brain parenchyma can be a target for transcranial US treatment of AIS. This possible effect of US was first described by Suchkova et al. [39]; this effect may also be achieved with US combined with microspheres [6].

Conclusion

Several clinical studies have shown that sonothrombolysis using ''diagnostic'' transcranial US in combination with rtPA improves recanalization of an acute intracranial artery occlusion. The chance of a favorable functional outcome after 3 months is doubled with this method of treatment when compared with rtPA treatment alone. TCCS has several advantages (e.g., visualization of an occlusion in a shorter insonation time) over TCD; thus, it is considered a more advanced tool. Although results of sonothrombolysis with TCCS have thus far been based on limited sample size, this method seems to provide a degree of effectiveness in achieving early recanalization of proximal MCA main stem occlusion that is similar to that provided by intra-arterial thrombolysis. For this reason, sonothrombolysis using TCCS should be considered an alternative treatment to intra-arterial recanalization procedures. A tendency toward increased cerebral infarction bleeding in patients treated with sonothrombolysis in combination with IV rtPA has not been confirmed thus far. Sonothrombolysis with TCCS alone in cases of contraindication for rtPA administration should be considered as a treatment option. Several studies have shown that microspheres may have a dual role: They may be used to enhance the effect of sonothrombolysis and assist in targeted drug delivery. To date, transcranial US has mainly been developed for diagnostic purposes. Several experimental studies have been conducted or are being undertaken to optimize US settings for sonothrombolysis. A need still exists to determine the optimal US frequency and energy so as to achieve the safest and most effective form of US for sonothrombolysis.

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