CAN ULTRASOUND ENHANCE THE RECANALIZATION EFFECT OF TPA? NO

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Stroke is the second most common cause of death and the major cause of disability in the world. In acute stroke, reperfusion therapies, including the intravenous use of rt-PA, have been shown to significantly improve the outcome in selected patients. However, intravenous administration of rt-PA results in partial or complete recanalization in only 30% to 50% of acute stroke patients. Since early and complete recanalization has been demonstrated as the most important predictor of good clinical outcome, efforts are being made to accelerate recanalization, and to increase complete recanalization rates. In order to improve the efficacy of reperfusion therapy, several new methods have been introduced in the past decades, including intra-arterial thrombolysis, endovascular treatment, ultrasound enhanced thrombolysis, as well as use of new thrombolytic agents. The main advantages of ultrasound enhanced thrombolysis comparing with the invasive procedures are that this method is simple, widely available, and does not delay the initatiation of the treatment.
Ultrasound energy has been shown to facilitate the effect of rt-PA during systemic intravenous thrombolysis, which effect is further enhanced by simultaneous administration of ultrasound contrast agents. Interestingly, ultrasound and ultrasound contrast agents have been reported to induce clot lysis even in the absence of rt-PA. Although several randomized studies proved that application of ultrasound energy enhanced the effect of rt-PA during intravenous thrombolysis, the most recent guideline (American Stroke Association guideline, 2013) suggests that

„the effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established (Class IIb; Level of Evidence B)".

This statement is in agreement with the last Cochrane review of „Sonothrombolysis for acute ischaemic stroke", which concludes that

„there is insufficient evidence to establish the effectiveness and safety of sonothrombolysis in routine clinical practice".

In the next paragraph arguments supporting the above cited statements are listed.

1) Effect of ultrasound administration on recanalization and clinical outcome was investigated in only 5 randomized trials with only 233 patients. Although the ultrasound frequencies were quite similar in the different studies (1.8 and 2.0 MHz), the trials showed differences in some other aspects: a) the time window for thromobolysis varied between 3 and 6 hours; b) the additional therapy besides ultrasound application was variable (ultrasound alone versus no treatment, ultrasound + rt-PA versus rt-PA alone, ultrasound + rt-PA + ultrasound contrast agent versus rt-PA alone); c) the duration of ultrasound administration varied between 1 hour and 2 hours.
2) Although some of these randomized studies proved that ultrasound application improved the recanalization rate, none of these studies showed a significant difference for the death and death or disability at 3 months after the treatment. It has to be mentioned, however, that when meta-analysis of these randomized clinical trials was performed, beneficial effect of sono-thrombolysis on recanalization rate and on disability or death at 3 months was found. Meta-analysis also showed a non-significant trend for increasing cerebral hemorrhages when ultrasound was administered, and the mortality rates were found to be quite similar between groups with or without ultrasound application.
3) Because ultrasound enhanced thrombolysis was associated with non-significant trend for increased risk of cerebral hemorrhage, there is an ongoing debate about the safety of ultrasound administration. Although 2 MHz ultrasound appeared safe during sonothrombolysis, application of low frequency ultrasound (300 kHz) significantly increased the risk of cerebral hemorrhage. Moreover, a meta-analysis of randomized sonothrombolysis studies showed that sonothrombolysis combined with simultaneous administration of ultrasound contrast agent (rt-PA+ultrasound+ultrasound contrast agent) significantly increased the rate of cerebral hemorrhage when compared to rt-PA treatment alone.

In summary, efficacy and safety of sonothrombolysis have been investigated by only few randomized controlled studies with small number of patients. Although meta-analysis of randomized sonothrombolysis trials showed promising results, the different study plans make difficult the interpretation of the findings. Concerning the clinical outcome, none of the randomized studies has proved a significant improvement for the death and death or disability at 3 months after the treatment. Moreover, there is a debate about the safety of ultrasound administration that may increase the risk of cerebral hemorrhage.
Sonothrombolysis is a promising therapeutic intervention for treating acute ischaemic stroke. Now, it seems that ultrasound enhanced thrombolysis without administration of ultrasound contrast agent increases the recanalization rate and sonothrombolysis increases the chance for independent survival without an increased risk of cerebral hemorrhages. However, further studies with more patients are needed to provide conclusive findings. According to this requirement, a phase 3, multicenter, randomized, double-blind trial, the so called CLOTBUSTER Trial for the Treatment of Ischemic Stroke has been in progress. The trial was designed to randomize up to 800

ischemic stroke patients on a 1:1 basis to either ultrasound treatment in combination with intravenous rt-PA therapy or standard intravenous rt-PA therapy alone. Hopefully, this study will answer the arising questions of sonothrombolysis.

Literature:

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