Sonothrombolysis and local drug delivery

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Fibrinolytic treatment uses enzymes such as recombinant tissue plasminogen activator (rt-PA), urokinase and streptokinase. These drugs have shown good efficacy (up to 30-40% when used intravenously, iv). Studies conducted over the past decade have aimed to optimise the efficacy and reduce the side effects of these treatments, focusing on new and safer fibrinolytics, optimisaton of dosages, and evaluation of the efficacy of combined therapy (fibrinolytics with anti-coagulants and anti-platelet agents).
The prevalent opinion is that a tailored adjuvant treatment capable of potentiating enzymatic thrombolysis, even via "non-enzymatic" pathways, is necessary to increase the success rate. One possibility is the use of ultrasound (US) as a means of promoting faster dissolution of the clot. Studies have explored both invasive and non-invasive ways of using US. One example is the use of miniaturised endovascular catheters with ultrasonic microprobes (1).
Lynn and colleagues were among the first to establish that US could be used to therapeutic ends. In the early 1940s, they clearly demonstrated that high-intensity and focalised US could cause site-specific tissue damage, without side effects in surrounding or superficial tissues. Nowadays, US has many therapeutic applications in the field of medicine, e.g. in the removal of dental plaque and the treatment of renal calculus (lithotripsy). Research efforts and experimental trials are currently focusing on the possibility of realising, through US, delivery of specific drugs (or gene products) to the target organ (local drug delivery or sonoporation). In addition, study of the use of US to potentiate rt-PA-mediated enzymatic thrombolysis is now in its advanced phase.
The main factor in the therapeutic effect is the beam energy, which determines the level of stress to which the insonated medium is subjected; the propagation of this stress results in the transfer of a certain amount of energy to the medium. As US waves propagate in a medium, the acoustic wave amplitude progressively decreases, as a part of its energy is transferred as heat. This portion of delivered energy is completely useless from a therapeutic point of view; in fact, it can sometimes be dangerous. A small part of the energy is transferred as mechanical energy and this, instead, can be exploited for therapeutic purposes; although it is only a small amount, in certain conditions it can be increased. "Henry's Law" (on the behaviour of gases in a liquid medium) can help us to imagine not only the thermal transformation of US waves in the medium, but also this "mechanical transformation". US waves crossing a solution (e.g. the blood in a blood vessel) may induce, briefly, the formation of gas microbubbles, mainly during the negative phase of the pressure wave. While to a large extent the bloodstream overheats, a small portion of the energy, the "mechanical" energy, will be absorbed by the gas molecules dissolved in the blood. These will thus pass briefly to the gaseous state, before quickly becoming dissolved again. Basically, gaseous molecules behave as "microcondensers" that absorb a small amount of energy and quickly transfer it back to the blood, thus producing a microstream (in proximity to the thrombus). This physical phenomenon is called acoustic cavitation (2). The US waves, in this way, increase the amount of the thrombolytic drug entering the clot, and favour a stronger action of tissue plasminogen activator (tPA) on the thrombus. This "sonothrombolytic activity" continues inside the clot, where the implosive collapse of the gaseous microbubbles destructures fibrin strands (non-inertial cavitation). Finally, mechanical agitation can expose shallow layers of thrombi to circulating tPA and

facilitate streaming of plasma through the thrombus, thereby delivering more tPA to the binding site. Therefore, when using echographic contrast agents, we get a natural increase of this sonothrombolytic activity. Some clinical trials were performed during the late 1990s. The ACUTE study, in patients with acute myocardial infarction, evaluated sonothrombolytic paradigms after conventional pharmacological thrombolysis. In much of the sample, an increase of the flow was obtained, which was then stabilised by balloon angioplasty. The most important published study is the CLOTBUST (Combined Lysis of Thrombus in Brain ischaemia using 2 MHz transcranial Ultrasound Systemic TPA) study, performed by Alexandrov and colleagues in open-trial, and then as a multicentre trial (CLOTBUST-II) (3). All the enrolled patients were submitted to the conventional treatment for acute ischaemic stroke (iv thrombolysis), but half of them received 2 hours' insonation (from the beginning of the thrombolysis), while only a rapid diagnostic transcranial Doppler (TCD) was performed on the remaining subjects. The results showed a good safety profile for the combined treatment; furthermore the clinical and functional efficacy was higher than in the single (conventional) treatment.

The German multicentre ARTHUS study, which used transcranial colour-coded Doppler (TCCD) instead of TCD, was a similar trial. In this study the combined treatment was confirmed as a superior therapy, but a troublesome increase of the haemorrhagic transformation rate was underlined. Moreover, the TRUMBI trial (4) was interrupted due to an unexpectedly high rate of haemorrhage (mainly asymptomatic). The negative results of these two trials were attributed to excessive acoustic power of the transducers compared to the CLOTBUST trial. On the other hand, recent studies performed by Alexandrov and Molina confirmed the efficacy and safety of sonothrombolysis, especially in presence of echocontrast agents. The most recent data (TUCSON study, 2009) (5) show that not all types of US insonation are adequate for therapeutic use, with TCD seeming to be preferable (greater efficacy and safety) to TCCD, and that the use of echocontrast agents (microbubbles, or more recently, nanobubbles) is key for maximising efficacy and reducing side effects (6).

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