

## **AUGMENTATION OF BLOOD FLOW IN ACUTE STROKE IMPROVES OUTCOME-NO**

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The development of brain infarction after the compromise of blood flow to the involved brain arterial territory is dependent upon many factors but the most critical factor is the severity and extent of the blood flow reduction. The ischemic region with the most severe blood flow reduction is the ischemic core and this region becomes irreversibly compromised rapidly after the onset of ischemia (1). The ischemic core is not the target of acute stroke therapy because interventions cannot occur rapidly enough to save this region. Ischemic regions with more modest blood flow reductions, estimated to be in the range of 12-30 ml/100gms/min from PET studies in both animal stroke models and humans can survive for an extended time period after ischemia begins (2). Regions of blood flow in this range identify the ischemic penumbra and this tissue can potentially be partially salvaged with timely reperfusion by i.v. tPA or an endovascular therapy. The availability of collateral blood flow channels to direct and augment blood flow into to the ischemic region can enhance the ability of ischemic tissue to be in the ischemic penumbra versus the ischemic core. The development of advanced imaging techniques such as diffusion/perfusion MRI and perfusion CT have provided the opportunity to approximate the location of and extent of the ischemic core and penumbra in stroke patients (3). On diffusion/perfusion MRI, the ischemic penumbra is best approximate as that region that is abnormal on the perfusion study, probably best identified with Tmax values, that does not demonstrate abnormality of diffusion imaging (4). On perfusion CT, the ischemic penumbra is approximated as the region with abnormal cerebral blood flow where cerebral blood volume has not yet collapsed. Thresholding of blood flow and blood volume abnormalities on CT perfusion is more problematic than thresholding of diffusion/perfusion abnormalities, so currently the later technique is much preferable for penumbral identification in clinical trials and practice(5).

The ability to approximate the extent and location of the ischemic core and penumbra on clinically available imaging modalities has potential applications for evaluating and developing acute ischemic stroke therapies. Additionally, with a largely experimental perfusion MRI technique, arterial spin-labeling, the contribution of collateral pathways to brain perfusion after focal arterial occlusion can be identified (6). A basic premise is that with better collateral flow after a proximal large artery occlusion more penumbra should be present for a longer time period. An obvious therapeutic approach would be to enhance collateral flow by pharmacological and/or mechanical approaches. Blood pressure augmentation by pharmacological means could potentially increase blood flow and small case series suggest that this approach may improve the outcome after ischemic stroke (7).

The mechanical device approach to blood flow augmentation was evaluated in the SENTIS trial (8). In this trial ischemic stroke patients within 14 hours of onset and an NIHSS of 5-18 were randomized to partial occlusion of the abdominal aorta for 45 minutes or standard medical therapy. The primary outcome measure was the stringent global disability assessment used in the NINDS tPA trials, NIHSS 0-1, mRS 0-1, Barthel Index 95-100 and Glasgow Outcome scale equal to 5 at 90 days. Serious adverse events (SAEs) were evaluated in both groups. Randomization led to 257 control patients and 258 actively treated patients in the intention to treat analysis with 249 and 254 patients ultimately available for outcome evaluation. The mean time from onset to randomization was 8.1 hours. The primary efficacy global outcome OR was 1.23 (CI 0.87-1.76, p=0.245). After enrollment 28 patients were excluded for prespecified exclusion criteria and in this modified intention to treat population the OR was 1.17 (CI 0.81-1.67, p=.407). The number of SAEs was very similar in the two treatment groups. None of the subscales evaluated for the efficacy assessment showed a significant difference between the two treatment groups. Acute improvement at 24 hours and the mRS dichotomized 0-2 versus 3-6 did not show significant differences between the treatment groups, although a small trend towards better outcome with treatment was observed. Deaths that was attributable to stroke occurred in 7.4% of the treated group and 14.4% of the controls. Interestingly, patients aged 70 or older about half the enrolled patients, had a favorable outcome when the mRS was dichotomized 0-2 and 3-6, OR 2.02 (CI 1.02-4.03, p=0.044). Patients treated within 5 hours from stroke onset were also significantly benefitted by treatment and those with a baseline NIHSS of 8-14 barely missed having a significant treatment effect on the mRS dichotomization.

The results of the SENTIS trial do not confirm that blood flow augmentation improves the outcome of acute ischemic stroke patients treated within 14 hours of onset. The results are however interesting and suggest that future studies of this treatment approach should be performed. It is entirely plausible that

the treatment effect observed when treatment was initiated within 5 hours of stroke onset may be replicated in a significant manner in another study within this time window. It reinforces the often quoted adage that time is brain. Enhancing collateral blood flow early after stroke onset could salvage part of the ischemic penumbra by allowing for endogenous thrombolysis to occur later after stroke onset. Additionally, the observation that blood flow enhancement appears to have some benefit in patients aged 70 or older also is plausible. In younger stroke patients we would expect better natural collaterals so that augmentation of collateral flow is not necessary as it would be in older patients in whom collateral channels are impeded by chronic hypertension, diabetes, hypercholesterolemia, etc. In conclusion, the well designed and implemented SENTIS trial did not confirm that mechanical enhancement of blood flow improved outcome in a diverse patient population treated on average relatively late after onset. The trial does however raise some interesting hypotheses that should be explored in future trials.

#### **References**

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