IS HEMOSTATIC THERAPY THE MOST PROMISING TREATMENT OPTION FOR ICH? – YES

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Background: Intracerebral hemorrhage (ICH) accounts for 10-15% of all stroke cases in Caucasian populations, and its rate is twice as high in Asia. ICH is a life threatening condition: 30 to 55% of the patients are dead 1 month after the stroke, and most fatalities occur in the first 2 days after the onset of ICH. Progression of the neurological signs is observed in every third patient within 2 days after the onset of ICH, and almost half of these patients with worsening stroke in the hyperacute phase do not survive the first month after their stroke. The expansion of the hematoma is frequent: appears in 20-40% in the first 3 hours and in about 70% of patients within the first 24 hours. From these numbers an ongoing bleeding even after the 3rd hour of the onset of ICH can be assumed – offering a clinically realistic time window for intervention. Hematoma enlargement is a major predictor of early case fatality and also of neurological deterioration in the acute phase of the disease. Halting the expansion of the hematoma therefore seems a reasonable therapeutic approach in ICH.

Evidence to date: both medical and surgical interventions have been tested to date in clinical trials aiming to inhibit hematoma growth. As an intracranial space occupying lesion, the most obvious approach to treat ICH is surgical evacuation. There are clear indications for surgery in infratentorial - mostly cerebellar - ICH. In supratentorial ICH the Surgical Trial in Intracerebral Hemorrhage (STICH) has been the largest trial to date to test if early surgery yields better results than early conservative treatment. In this study of over 1000 patients good outcome was found in 26% and 24% of those treated surgically and medically, with no statistically significant difference between the 2 groups. A systematic review of 10 trials comparing surgical and medical interventions suggested better outcome after surgery, but no strict indications for surgery are given in current guidelines for supratentorial ICH. Stereotaxic aspiration of the hematoma with or without the local administration of a thrombolytic agent may also be promising, however no large trials have been completed to date. Hemostatic therapy aims to stop bleeding in intracerebral hemorrhage thus blocking the expansion of the hematoma. Initially, epsilon aminocaproic acid was used for this purpose, however the only randomized clinical trial was stopped prematurely due to low inclusion rate. There is an ongoing trial with tranexamic acid. There are completed and ongoing trials with recombinant activated 7th coagulation factor (rFVIIa). The first relatively large phase 2b clinical trial on hemostatic therapy tested the effect of rFVIIa to evaluate if such treatment improves short- and long-term outcome in ICH. In this double-blind, placebo-controlled trial 399 patients were included at 73 hospitals in 20 countries. Growth in the volume of the hematoma was significantly smaller, and death or disability was significantly less frequent in the treatment group. Case fatality 3 months after stroke was also significantly less in those treated with rFVIIa compared to placebo. This first relatively large study on rFVIIa in ICH therefore showed at a statistically significant level that rFVIIa not only decreases the expansion of ICH but results in clinically and statistically significant benefit in clinically important end-points. To confirm these findings, the study was repeated at a phase 3 level (the FAST trial) and included 841 subjects. This study confirmed the beneficial effect of rFVIIa on hematoma growth. Interestingly, despite this reduction in bleeding expansion, there was no significant difference among the groups in the proportion of patients with poor clinical outcome. An imbalance in prognostic factors between study groups in favor of those receiving placebo, should be noted. A Cochrane review of 6 clinical trials in 1400 subjects reported a 9% decrease in the risk of death or disability and a 15% decrease in case fatality in those treated with rFVIIa compared to placebo, however, the difference did not reach statistical significance.

Conclusions: In summary, ultra-early hemostatic therapy with rFVIIa limited the growth of hemorrhage, reduced case fatality, and improved functional outcomes after ICH in an international multicenter, randomized, placebo controlled phase 2b trial. In a further larger phase 3 trial (FAST) the rFVIIa dose of 80 ug was associated with a significant reduction of hematoma expansion as well. Two independent randomized studies in ICH therefore already confirmed the reduction in hematoma volume expansion after hemostatic treatment with rFVIIa. All the randomized data are currently from less than 1500 patients which number is small to come to an unequivocal conclusion. As ICH volume expansion has been found to be a strong prognostic indicator in several studies, considering all the information to date, hemostatic treatment should be considered a promising approach and a large study with stratified randomization should be performed to come to a final conclusion.