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Comparative Effectiveness of Haemostatic Therapy in Experimental Warfarin-associated Intercerebral Hemorrhage

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Intracerebral hemorrhage associated with oral anticoagulants (OAC-ICH) is a growing problem without a clear solution. Hematoma growth is considered as a major threat that worsens prognosis. Current treatment guidelines are based on case series and plausibility only, and a common consensus on effective hemostatic therapy is missing. Herein, we refined a mouse model of OAC-ICH using repetitive T2* MRI to describe kinetics of hematoma enlargement, and established a benchside point of care INR assay (PoC) for assessment of anticoagulation. Thereafter, we compared the effectiveness of diverse hemostatic approaches in a mouse model of warfarin-associated ICH (W-ICH).

The major new findings of our study are that: (1) Hematoma expansion in this OAC-ICH model occurs predominantly in the first 1–3 h. (2) PCC and FFP are equally effective in preventing hematoma growth in experimental W-ICH, whereas FVIIa is less potent. (3) TA also has an intermediate hemostatic effect, but it substantially increases edema formation (4) Effective reversal of the anticoagulatory effect of warfarin as measured by INR is a good predictor of final hematoma size.

Our findings have implications for the experimental examination of OAC-ICH and potentially provides some translationally useful information. A prerequisite for the timing of the administration of an experimental hemostatic substance is to know the kinetics of OAC-ICH expansion in the model. In the clinical setting, orally anticoagulated patients more frequently suffer prolonged or repetitive hemorrhage compared to non-anticoagulated patients (Aguilar et al., 2007). In our model hematoma enlargement mainly occurred within the first hour, and 95% of maximal hematoma value was reached already 3 h after collagenase injection. Consequently, any hemostatic therapy can only prevent hematoma expansion in this experimental model when treatment is initiated within the first 3 h, and

ideally within the first hour after ICH induction. Moreover, our findings reveal important differences regarding the effectiveness and side effects of common hemostatic agents in experimental W-ICH. PCC and FFP appear to be the more effective agents to reverse the anticoagulatory effect of warfarin and thereby prevent secondary hematoma enlargement. FVIIa is less effective. Currently, a phase III clinical trial is conducted to resolve which of the two best hemostatic agents more rapidly antagonizes the anticoagulatory effect of warfarin in the setting of ICH.