Analysis of Acute Perihematomal Edema in Warfarin-Related Intracerebral Hemorrhage

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Background: Little is known about the mechanisms of acute edema formation around a hematoma in intracerebral hemorrhage (ICH). Gebel et al, Stroke (2000) showed that there is significantly decreased hyperacute perihematomal edema in thrombolysis/anticoagulant–related ICH compared to spontaneous ICH. Multiple animal models have suggested that successful clot formation is required for the development of acute perihematomal edema. These observations led to the hypothesis that acute perihematomal edema is osmotic in nature and reflects clot integrity. That is, as a hematoma forms, proteins in the serum exude out from the hematoma and act as osmotic agents, drawing fluid toward them and causing perihematomal edema. If this hypothesis is true, it would suggest that the edema is a reflection of how well-formed the clot is. It may therefore, seemingly paradoxically, be a predictor of better outcome. Gebel et al, Stroke (2002) showed that hyperacute perihematomal relative edema was a strong, independent predictor of 3-month functional outcome (increased relative edema, decreased odds of poor outcome).

Objectives: We sought to test this hypothesis by determining whether there was a relationship between INR and acute edema volume and whether edema predicted mortality. We also wanted to explore whether any other factors correlated positively or negatively with edema volume. Our main hypothesis: INR is negatively correlated with edema volume.

Methods: We performed a retrospective observational study of 49 consecutive warfarin-related ICH cases that presented to the Massachusetts General Hospital Emergency Department between 10/98 and 4/04 to determine the predictors and outcomes related to acute perihematomal edema. Initial CT Scans of patients taking warfarin with supratentorial ICH were analyzed using Alice software. ICH volumes and volumes of perihematomal edema were measured. Patient information was obtained from the Clinical Trials Unit database, and the following predictors of ICH and edema volumes were examined: age, PT, aPTT, INR, platelet count, SBP, DBP, serum glucose, gender, hx CAD, hx ischemic CVA, DM, antiplatelet use, location of ICH, and APOE ε genotype. All statistical analyses performed were nonparametric, because the outcomes of interest were not normally distributed.

Results: 49 consecutive cases of warfarin-related supratentorial ICH that presented to Massachusetts General Hospital were examined. Population characteristics were as follows, with mean and (standard deviation): age 76.8 years (8.4), INR 3.8 (2.3), admission SBP 173.4 mm Hg (36.5), admission DBP 91.5 mm Hg (19.6), blood glucose 151.4 mg/dl (45.5), symptom
onset to scan time 6.5 hours (7.9), ICH volume 55.5 cc (55.9), and edema volume 22.1 cc (25.1). Other characteristics of the population include 59.2 % female, 36.2 % with a history of CAD, 18.8 % with diabetes mellitus, 45.2 % with a history of ischemic stroke, 40.8 % with antiplatelet use, 60.7 % homozygous for the APOE ε3 allele, and 46.9 % with a lobar location of bleeding (versus deep). In terms of ICH volume, a few significant relationships were found: A positive correlation between blood glucose and ICH volume ($r = 0.408$, $p = 0.005$). A positive relationship between lobar location and ICH volume (lobar: mean volume 76.9 cc ± 12.6, deep: mean volume 36.6 cc ± 8.7, $p=0.012$). A positive relationship between antiplatelet use and ICH volume (antiplatelet use: mean volume 77.9 ± 13.2, no antiplatelet use: mean volume 40.1 ± 9.1, $p=0.007$). In terms of edema, absolute edema is defined as the total amount of edema around the hematoma. Relative edema is defined as the volume of edema divided by the volume of the hematoma. Significant relationships found for absolute edema were: A positive correlation between absolute edema and ICH volume ($r = 0.924$, $p<0.001$). A positive relationship between absolute edema and antiplatelet use ($p=0.019$). A positive correlation between blood glucose and absolute edema ($r = 0.275$, $p=0.058$). Significant relationships found for relative edema were: A negative correlation between relative edema and blood glucose ($r = -0.316$, $p=0.029$). There was a non-significant negative correlation between relative edema volume and INR ($r = -0.237$, $p = 0.106$). A linear regression model for absolute edema volume was constructed using the following independent variables: ICH volume, blood glucose, SBP, DM, INR, antiplatelet use. Of these, the following were found to be independent predictors of absolute edema volume: ICH volume ($r = 0.969$, $p<0.001$), blood glucose ($r = −0.127$, $p=0.043$), and systolic BP ($r = −0.112$, $p=0.061$). In logistic regression models, ICH volume appears to be the only significant independent predictor of in-hospital and one month mortality.

**Discussion / Conclusions:** These analyses yield some interesting data in relation to hematoma and edema volumes in warfarin-related ICH. First, our initial hypothesis was not supported. The relative amount of edema was not significantly correlated to INR. A negative trend existed, but the p value was 0.106. Thus, this does not support the original hypothesis of perihematomal edema being osmotic and reflecting clot integrity, since increasing INR should make the blood less likely to clot. At the start of this project, we did not know what the relationship between ICH volume and absolute edema volume would be like. It could be hypothesized that edema formation is based on surface area of the hematoma, and thus larger ICH volumes, which have a smaller ratio of surface area to volume, might have less relative edema. However, our data strongly suggest otherwise. We show a strong positive correlation between absolute edema volume and ICH volume. When this data is plotted, a linear relationship is observed. Thus, the relative amount of edema does not appear to differ in small vs. large hemorrhages. Absolute edema does appear to correlate strongly with hematoma volume. Another interesting finding is in relation to blood glucose. Song et al, *Stroke* (2003) developed a rat model of ICH. They found that hyperglycemic animals had significantly increased brain water content compared to controls. High blood glucose would be expected to correlate with increased edema, since glucose is an osmotic particle. Our findings showed a strong positive correlation between glucose and ICH volume in univariate analysis, a positive non-significant correlation between glucose and absolute edema volume in univariate analysis, and a negative correlation between glucose and relative edema volume in univariate analysis. In multivariate analysis, blood...
glucose was a negative, independent predictor of both absolute and relative edema. Since glucose is strongly correlated with ICH, and absolute edema is strongly correlated with ICH, the relationship between glucose and absolute edema in univariate analysis is likely caused by these relationships. In the multivariate regression models, however, it appears that glucose independently and negatively predicts edema formation. The biologic cause of this is unknown. It is important to note that this is a correlation, not a cause and effect. The correlation between antiplatelet use and increased ICH volume in people taking warfarin is also of note. However, this was not found with larger sample sizes in previous studies by our group. This will have to be looked into further. Finally, we have found ICH volume to be the only independent predictor of in-hospital and one month mortality. One possible limitation of this study relates to the feasibility of measuring edema on CT scan. Perihematomal edema was considered as the hypodense area around the hematoma. This is often difficult to see visually, so hounsfield unit measurements were used to confirm visual tracings. Yet other factors, such as periventricular white matter disease, produce hounsfield units of a similar range. A potential biasing factor was the fact that no exclusions based on time from symptom onset to CT scan were used. The average time was 6.5 hours, but in several instances the time of symptom onset wasn’t known, and these times were probably a lot longer. Since hyperacute vs. acute vs. subacute edema volumes may differ, this could be an important bias. Future directions could include measuring edema volumes on non-warfarin patients and doing comparisons between the two groups. Also, more standardized time constraints could be looked at in the future. Finally, we could perform edema volume measurements on MRI.