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MAPPING THE ANTIFIBRINOLYTIC WINDOW: TIME-DEPENDENT OUTCOME PATTERNS AND HAEMORRHAGE PHENOTYPES IN TRAUMATIC BRAIN INJURY

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Relevance. Traumatic brain injury (TBI) causes over 10 million deaths and hospitalizations annually. The CRASH-3 trial demonstrated a mortality signal favoring early treatment with tranexamic acid (TXA) in TBI, which is consistent with TXA's time-dependent antifibrinolytic mechanism, particularly in mild to moderate injury. However, whether the time-dependent outcome pattern varies across clinical subgroups, and whether the CT-defined hemorrhage phenotype independently determines functional recovery, remains uncharacterized in this dataset.

Aim: to characterize the independent association between time to treatment and mortality using the blinded CRASH-3 dataset; test whether this effect is modified by the injury subgroup; and examine how the intracranial hemorrhage subtype predicts functional independence at discharge, generating pharmacological hypotheses.

Materials and methods. A secondary analysis of the blinded CRASH-3 dataset (n = 12,743) was carried out. 28-day mortality was modeled against time-to-treatment, (n=12,568 after excluding missing data) GCS, age, and pupillary reactivity, with interaction terms for all subgroups. Among CT-scanned patients with confirmed intracranial bleeding (n = 8,652), hemorrhage subtype prevalence (epidural, subdural, subarachnoid, parenchymal, and intraventricular) was examined across all levels of functional independence at discharge. Further, research was supplemented by scientific literature.

Results and their discussion. In the mortality model, each hour of treatment delay independently increased mortality odds by approximately 3% (OR 1.03, 95% CI 1.00-1.06, $p = 0.04$), which is consistent with a narrowing antifibrinolytic window as fibrinolysis resolved post-injury. GCS was the strongest predictor (OR 0.78, $p < 0.001$), and non-reactive pupils conferred approximately 5 times higher mortality odds (OR 4.71, $p < 0.001$). Critically, no significant interaction was found between time and any subgroup (GCS, pupils, or age; all $p > 0.05$), indicating the fibrinolytic surge is uniform across injury severity, supporting the broad treatment window.

Upon modeling the hemorrhage phenotype, subarachnoid hemorrhage showed the steepest functional gradient (42.1% in independent vs. 64.4% in totally dependent patients). Thus, it is theoretically the most responsive to treatment. Intraventricular hemorrhage, though rare, had the strongest relative gradient (1.8% vs. 11.8%; 6.5-fold) and represents a deep coagulopathic process. Epidural hemorrhage was inversely associated with dependency (26.6% vs. 14.9%), consistent with the fact that it's a less effective target for antifibrinolytics.

Conclusions. Treatment delay independently predicts TBI mortality uniformly across all patient subgroups, consistent with a time-sensitive antifibrinolytic pharmacodynamic window. Subarachnoid and intraventricular hemorrhages carry the greatest functional burden at discharge, while epidural hemorrhage is the most functionally favorable phenotype.