

Effects of Bilirubin Oxidation Products (BOXes) on White Matter Edema Development and Injury Following Intracerebral Hemorrhage

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Background: Delayed pathophysiological events contribute significantly to brain tissue injury from intracerebral hemorrhage (ICH), a stroke subtype with high mortality and morbidity. These delayed events are characterized by a breakdown of the blood brain barrier, edema development, and cell death. Bilirubin Oxidation Products (BOXes) underlie delayed pathophysiologic events after another stroke subtype, subarachnoid hemorrhage (SAH). BOXes production by the hematoma also occurs within the first 24 hours after ICH. This present study investigated the contribution of BOXes to white matter edema formation and perihematomal brain injury using a large animal (pig) model. The porcine lobar ICH model is well validated and especially useful for this study due to the pig's well developed white matter. **Methods:** BOXes (50 μ M) were directly infused into lobar white matter of deeply anesthetized 20 kg pigs at a rate of 1ml/hr for 3 hours using a physiological saline vehicle (n=5). Infusion of vehicle alone served as control (n=3). Dosage and time course were based on previously demonstrated *in vivo* and *in vitro* effects. Upon completion of BOXes infusion, Evans Blue (20 mL) was infused intravenously. Animals were monitored post-infusion for periods of 8 (BOXes n=1, Vehicle n=1) or 24 hrs (BOXes n=4, Vehicle n =2). Their brains were then frozen *in situ* and serially sectioned. Edema volume was determined by computer-assisted morphometry. Perihematomal brain injury was examined using standard immunocytochemical methods. **Results:** Edema volumes, and induction of heat shock proteins and inflammatory cytokines were similar between the two groups and were independent of time. **Conclusion:** Infusion of either BOXes or vehicle into porcine white matter induced injury. Additional studies are required due to the large standard deviations in edema volumes and small differences between the two groups. Further testing may demonstrate that the cortical vasculature is more vulnerable to BOXes toxicity than the deeper white matter vasculature.