**Resuscitation with drag reducing polymer after traumatic brain injury with hemorrhagic shock reduces microthrombosis and oxidative stress**

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**Abstract:** Outcome after traumatic brain injury (TBI) is worsened by hemorrhagic shock (HS), but existing volume expansion approach with resuscitation fluids (RF) is controversial as do not adequately alleviates impaired microvascular cerebral blood flow (mCBF). We previously reported that resuscitation fluid with drag reducing polymers (DRP-RF) improves CBF by rheological modulation of hemodynamics. Here, we evaluate the efficacy of DRP-RF, compared to lactated Ringers resuscitation fluid (LR-RF), in reducing cerebral microthrombosis and reperfusion mitochondrial oxidative stress after TBI complicated by HS. *Methods:* Fluid percussion TBI (1.5 ATA, 50 ms) was induced in rats and followed by controlled HS to a mean arterial pressure (MAP) of 40 mmHg. DRP-RF or LR-RF was infused to restore MAP to 60 mmHg for one hour (pre-hospital period), followed by blood re-infusion to a MAP=70 mmHg (hospital period). *In vivo* 2-photon laser scanning microscopy over the parietal cortex was used to monitor microvascular blood flow, NADH (hypoxia) and mitochondrial oxidative stress (superoxide by i.v. hydroethidine [HEt], 1 mg/kg) for 4 hours after TBI/HS, followed by Dil vascular painting during perfusion-fixation. Brain and rectal temperatures, MAP, blood gases and electrolytes were monitored. *Results:* TBI/HS decreased mCBF resulting in capillary microthrombosis and tissue hypoxia. Microvascular CBF and tissue oxygenation were significantly improved in the DRP-RF compared to the LR-RF treated group (p<0.05). Reperfusion-induced oxidative stress, reflected by HEt fluorescence, was 32 ± 6% higher in LR-RF vs. DRP-RF (p<0.05). Post-mortem whole-brain visualization of DiI painted vessels revealed multiple microthromboses in both hemispheres that were 29 ± 3% less in DRP-RF vs. LR-RF group (p<0.05). *Conclusions:* Resuscitation after TBI/HS using DRP-RF effectively restores mCBF, reduces hypoxia, microthrombosis formation and mitochondrial oxidative stress compared to conventional volume expansion with LR-RF.

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