Porcine Model of Early Cortical Infarction after Subarachnoid Hemorrhage

Christopher Patrick Carroll MD MA; Bryan Matthew Krueger MD; Eric J Mahoney MS; Jason Hinzman PhD; Jed Hartings PhD
Department of Neurosurgery and the Gardner Neuroscience Institute, University of Cincinnati

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Introduction

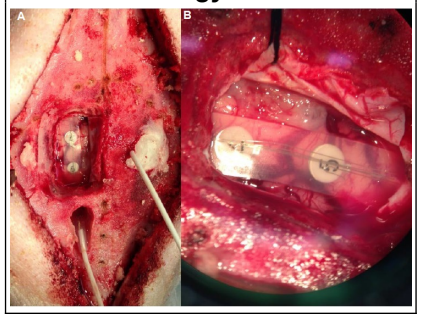
Aneurysmal subarachnoid hemorrhage (SAH) is associated with early cerebral infarction (ECI) and delayed cerebral infarction (DCI). Vasospasm can lead to cerebral infarction; not all DCI is seen in major arterial watersheds or in association with vasospasm. ECI is common in poor-grade SAH patients and characterized by laminar ischemic change in contiguous cortex. ECI is often seen adjacent to organized sulcal clot and often develops independent of cerebral vasospasm. Topical infusion of hemolysis products in Wistar rats led to cortical spreading depolarizations (CSDs), decreased cerebral blood flow, and spreading cortical ischemia. On pathologic examination, 50% of animals with CSDs demonstrated band-like ECI of adjacent cortex; no animals without CSDs had ECI. We previously developed the first gyrencephalic model of SAH, CSD, and ECI by performing subarachnoid infusion of fresh autologous blood in juvenile pigs. Organized sulcal subarachnoid clot was significantly associated with spontaneous, recurrent CSDs and ECI of adjacent cortex, but variable.

We refined our protocol to explore the relationship of sulcal subarachnoid clot, CSD, and ECI. We hypothesized that organized sulcal subarachnoid clot would result in significantly more CSD and ECI than surgical and mass effect controls.

Methods

Juvenile swine underwent frontal craniotomy and exposure of the cruciate sulcus. First, animals underwent sulcal injection of autologous blood clotted ex vivo (n=6). In the second experiment, animals were randomized to one of three experimental manipulations: sulcal infusion of 1mL normal saline (n=4), fibrin sealant (n=4), or autologous blood clotted ex vivo (n=5). Animals underwent six hours of electrocorticographic monitoring prior to sacrifice. Brains were then removed for TTC and H&E staining. Statistical analysis included one-way ANOVA with post-hoc analysis; the Spearmann's Rank Order correlation coefficient; and student's t-test.

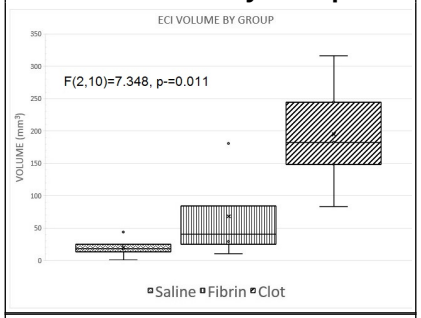
Surgical Technique and Gross Pathology on TTC



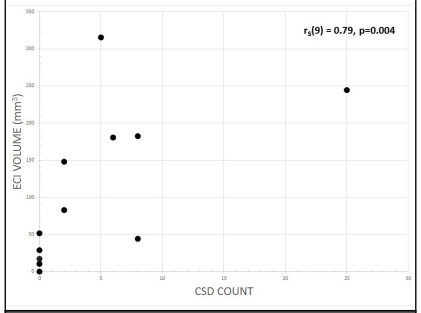
Results

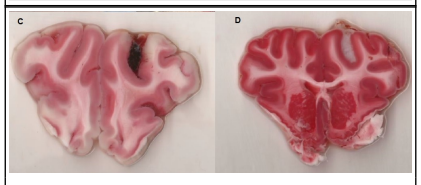
Sulcal clot injection resulted in CSDs in 83% (n=6; count range: 4-20). Persistent sulcal subarachnoid clot and ECI were seen in 100%. H&E staining demonstrated well-demarcated cerebral edema and ischemic neuronal injury. Animals were randomized to injection of normal saline (n=4), fibrin sealant (n=4), or autologous blood clot (n=5). Fibrin sealant and clot volumes did not differ (p=0.482). ECI volumes differed significantly between groups: saline (M=19.9 mm3, SD=18.0), fibrin sealant (M=67.8 mm3, SD=77.2), and autologous clot (M=194.6 mm3, SD=89.3) [F(2,10)=7.348, p=0.011]. Post hoc analysis demonstrated significantly larger infarct volumes for autologous clot versus saline (p=0.013) and fibrin sealant (p=0.048). Saline and fibrin sealant infarct volumes did not differ (p=0.364). CSD counts did not differ significantly: saline (M=2.7, SD=4.62), fibrin sealant (M=2.0, SD=3.46); and autologous clot (M=8.4, SD=9.61) [F(2,8)=0.927, p=0.434]. A two-tailed Spearmann's rank-order analysis demonstrated significant correlation between CSD count and ECI volume (rS(9)=0.79, p=0.004).

ECI Volume by Group



ECI Volume versus CSD Count





A, Craniotomy and ECOG placement. B, Fibrin sealant injection. C, TTC Stain, clot injection. D, TTC Stain, fibrin injection.

Conclusions

Organized sulcal clots cause adjacent cortical infarction, which cannot be attributed to surgical manipulation or mass effect alone. Further studies are needed to elucidate factors that trigger CSDs and ECI as well as to test pharmacologic targeting of CSDs in this gyrencephalic model of ECI after SAH.

Learning Objectives

(1) Describe cortical spreading depolarizations as they relate to aneurysmal subarachnoid hemorrhage.
(2) Discuss, the gyrencephalic porcine model of early cortical infarction after SAH and the relationship between sulcal subarachnoid clot, CSDs, and ECI.
(3) Identify CSD as a potential therapeutic target to reduce ECI after SAH.

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References

1. Dreier JP et al. Products of hemolysis in the subarachnoid space inducing spreading ischaemia in the cortex and focal necrosis in rats: a model for delayed ischemic neurological deficits after subarachnoid hemorrhage? J Neurosurg 93: 658-666.
2. Dreier JP et al. Cortical spreadin ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid hemorrhage. Brain 132: 1866-1881.
3. Dreier JP et al. Focal laminar cortical MR signal abnormalities after subarachnoid hemorrhage. Ann Neurol 52(6): 825-9.
4. Kistler JP et al. The relation of cerebral vasospasm to the extent and location of subarachnoid blood visualized by CT scan: a prospective study. Neurology 33(4): 424-36.
5. Schatlo B et al. Report of Selective Cortical Infarcts in the Primate Clot Model of Vasospasm After Subarachnoid Hemorrhage. Neurosurgery 67(3): 721-729.
6. Weidauer S et al. Focal laminar cortical infarcts following aneurysmal subarachnoid hemorrhage. Neuroradiology 50: 1-8.