

## CURCUMIN ATTENUATES HEMATOMA SIZE AND NEUROLOGICAL INJURY FOLLOWING INTRACEREBRAL HEMORRHAGE IN MICE

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## Causes/Risk Factors

- Risk factors: older age, male sex, hypertension, high alcohol intake (>2 drinks/day), >5 caffeinated drinks/day, caffeine in drugs, current cigarette smoking, diabetes, and menopause.
- Platelet aggregation inhibitors (Plavix, etc) and aspirin associated with an increased risk of cerebral microbleeds in older patients.
- Non-aspirin NSAIDS are NOT associated with increased risk of ICH.
- Liver cirrhosis and alcoholic liver disease also associated with increased risk of ICH OR 4.8.

## Intracerebral Hemorrhage

- Rupture of small arteries or arterioles leading to hemorrhage into brain parenchyma
- 50% of ICH occurs in the putamen (lenticulostriate branches) 20% thalamus, 10% cerebellum, 10% pons, 5% cerebral white matter (lobar hemorrhage)
- HTN is the most common cause
- Others include microangiopathy, occlusive hypertensive vascular disease, arteriolosclerosis



## Prognosis

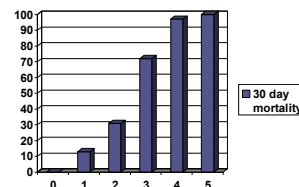
- Primary ICH has very poor short and long term outcome
- Mortality
  - 7.3% before hospital admission
  - 34.6% at 7 days
  - **50.6% within 28 days**
  - 59% at 1 year.
- Cumulative survival at 16 years 3.2% for men and 9.8% for women.
- Other predictors of poor outcome include: hemorrhage extending to SA or lateral ventricles, cerebellar hemorrhage, lobar hemorrhages >40 cm<sup>3</sup> with GCS <13, and regular ASA or Coumadin use at time of onset of ICH.
- **Hematoma volume directly correlates with neurological outcome**

## ICH incidence

- Occurs in > 120,000 Americans each year
- ICH accounts for 15-20% of all strokes each year
- Primary ICH: unrelated to congenital or acquired lesions. Accounts for 78-88% of hemorrhagic stroke
  - Hypertensive arteriolosclerosis
  - Amyloid angiopathy
- Secondary ICH: acquired or congenital lesions. Minority of cases
  - Coagulopathies
  - Brain Tumors
  - Aneurysms
  - Vascular Anomalies
  - Thrombolytic treatment of ischemic stroke

## ICH Score Predicts Mortality

- GCS 3-4= 2 points
- GCS 5-12= 1 point
- GCS 13-15= 0 points
- 1 point each for:
  - >80 y/o,
  - infratentorial
  - volume >30 cm<sup>3</sup>
  - intraventricular hemorrhage



**30-day mortality based on point score**

- 0 points: 0%
- 1 point: 3-13%
- 2 points: 26-31%
- 3 points: 61-72%
- 4 points: 88-97%
- 5 points: 100%

## Treatment: Medical

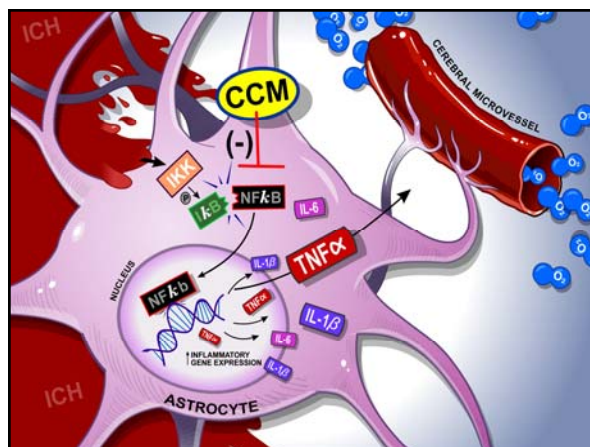
- ABCs. Give IV fluids and antiepileptic medication if indicated (for lobar hemorrhages), but always aggressively control BP, ICP, and hyperglycemia.
- Not enough evidence to support the use of mannitol after acute ICH.
  - No differences in rates of death, disability, or fatality rates between 3 separate trials.
- First clinical trial of rFVIIa (NovoSeven) showed that when given within 4 hours of the acute bleed, it significantly reduced expansion of the hematoma at 80 mcg/kg (-3.8 mL vs placebo,  $p=0.009$ ), and also appeared to modestly reduce mortality at 90 days (18% vs. 29%).
- Further trials (FAST trial) did not show any improvement in functional outcome or mortality when rFVIIa used to treat acute ICH.

## Hypothesis

*Curcumin will reduce the size of hematoma volume, limit the amount of inflammation and edema, and improve neurological outcome after induced ICH in mice*

## Treatment: Surgical

- General recommendations from STICH trial
  - Remove hemorrhage ASAP if CBL hemorrhage >3 cm with neurological deterioration, brainstem compression and/or hydrocephalus from ventricular obstruction
  - Craniotomy can be useful in treatment of lobar clots within 1 cm of the surface with GCS >9.
  - Further evidence is needed for recommendations of mechanical devices (stereotactics) or endoscopy, but there has been some promising results
  - Operative removal within 12 hours has the most supportive evidence, especially if by less invasive procedures. Ultra-early craniotomy does not appear to offer substantial benefit, and may increase risk of re-bleeds



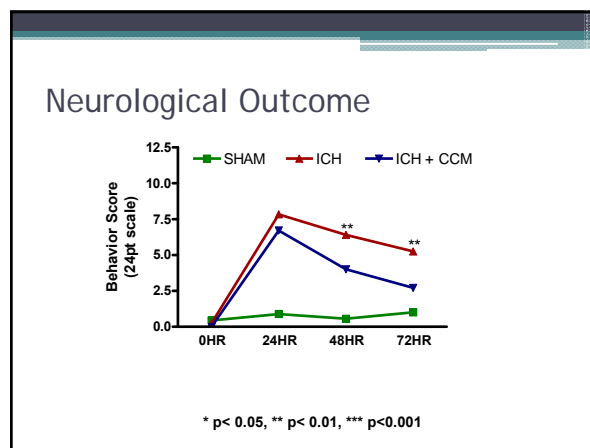
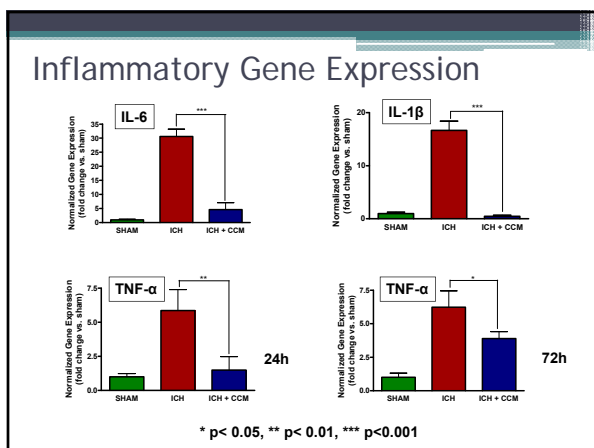
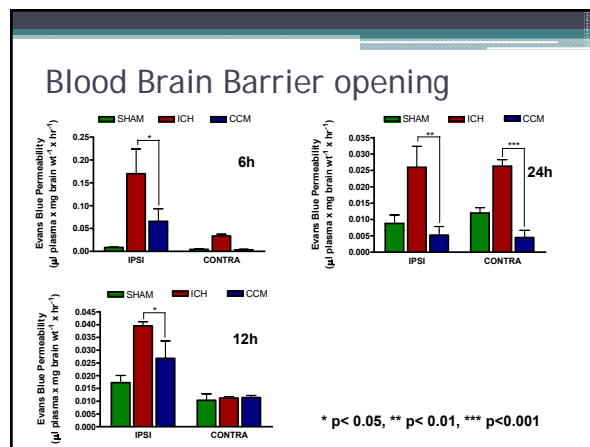
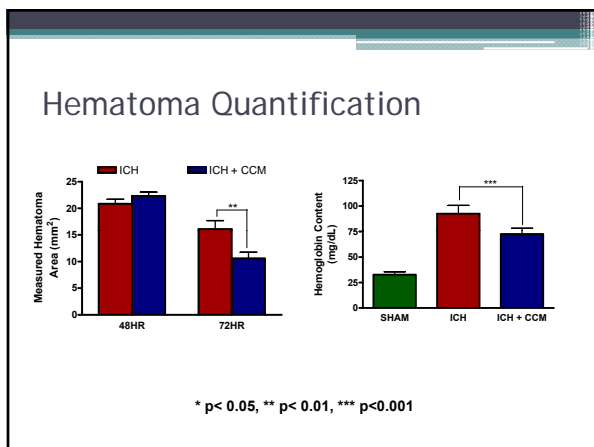
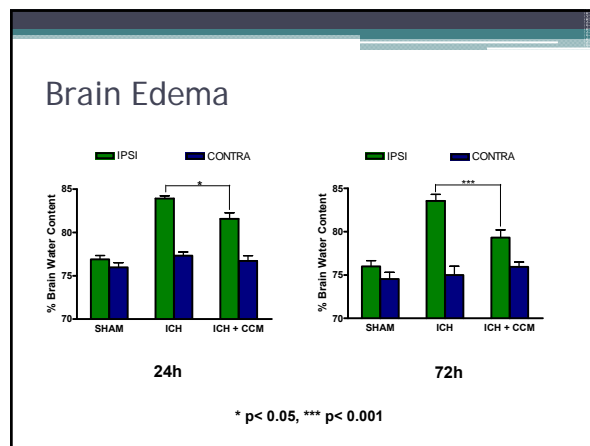
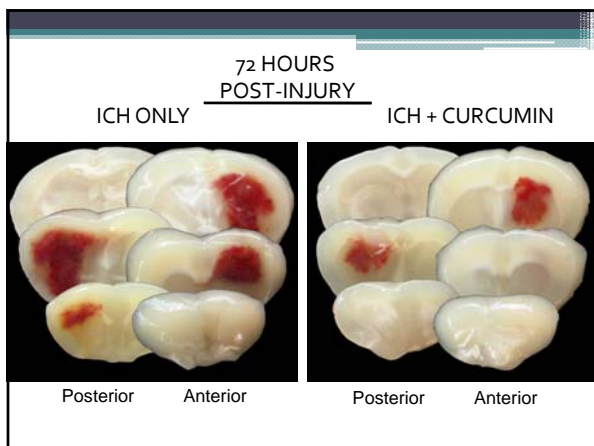
## Curcumin

- Used for centuries in Indian Ayurveda medicine in the treatment of wound-healing, ulcers, and arthritis
- Has significant antioxidant, anti-inflammatory, proliferative, carcinogenic, and angiogenic activity
- Recent clinical trials in patients with colon cancer, FAP, pancreatic cancer, and multiple myeloma
- Reduces oxidative damage and inflammation in animal models of Alzheimer's disease, TBI, ischemic stroke, and SAH
- Very safe when taken orally, with minimal side effects



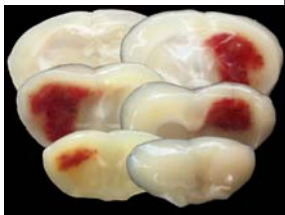
## Procedure





## Summary

- The final size of the hematoma after ICH stabilization is the best indicator of patient prognosis
- Curcumin grossly reduced the volume of hematoma and down-regulated pro-inflammatory gene expression, decreased edema, and improved neurological outcome by 72 hours post-ICH
- Curcumin may be a useful adjunct to both surgical and medical management of ICH patients



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## Future Directions

- Currently working on 30 different novel analogues of the curcumin molecule to increase potency and bioavailability
- Biodegradable curcumin nanoparticles used to increase the bioavailability and half-life, increase cellular uptake, and have a more potent anti-inflammatory effect than non-NP curcumin.
- PPAR $\gamma$  induced hematoma resolution pathway, the target of glitazone drugs and curcumin.

## References

- [Stroke 2009 Jun;40\(6\):1680](#)
- [Stroke 2005 Sep;36\(9\):1881](#)
- [Stroke 2009 Feb;40\(2\):324](#)
- [Neurology 2006 Aug 8;67\(3\):424](#)
- [Stroke 2005 Sep;36\(9\):1881](#)
- [Arch Neurol 2009 Jun;66\(6\):714](#)
- [Stroke 2003 Feb;34\(2\):387](#)
- [BMC Gastroenterol 2008 May 24;8:16](#)
- [Stroke 2009 Feb;40\(2\):324](#)
- [J Neural Neurosurg Psychiatry 2005 Nov;76\(11\):1534](#)
- [Cerebrovasc Dis 2001;11\(9\):185](#)
- [Stroke 2006 Jan;37\(1\):129](#)
- [Stroke 2001 Apr;32\(4\):891](#)
- [Stroke 2006 Apr;37\(4\):1038](#)
- [BMJ 2000 Nov 25;321\(7272\):1358](#)
- [N Engl J Med 2005 Feb 24;352\(8\):777](#)
- [N Engl J Med 2008 May 15;358\(20\):2127](#)
- [Stroke 2007 Mar 7;38\(3\):2091-2093](#)
- [Biochemical Pharmacology 2009, Sept 1; \(9\) 10317](#)
- [Aggarwal, B. Biochem Pharm. 2009, Sept 1, BCP-10317.](#)
- [Aronowski, J. Ann Neurology. 2007, 61:352-362](#)