Evidence based treatment of Vasospasm after aneurysmal SAH

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Introduction

- Case presentation to assist in the review of the VS
- Clinical presentation
- Pathophysiology
- Evidence based treatment of vasospasm
Patient

- MH 33 yo RH F, WHOL and syncope
- Smoker
- Dabbles in recreational drugs
- PMH HTN
- Obtunded and decorticating
Will RH experience vasospasm

- Narrowing of major intradural arteries near skull base, rarely affects distal vasculature
- Time course
  - Appears SAH day #3-4
  - Peaks SAH day #7-8
  - Resolution by SAH day #14
Steps often used to prevent/monitor for/treat vasospasm

- Early treatment of aneurysm (<24hrs)
- Ventriculostomy in poor grade or hydrocephalic pts
- 125 cc/hr; avoid dehydration
- Volume expansion w/colloid
- Maximize Starling curve
- Hematocrit >10
- TCDs bid
- Decadron
- Nimodipine
- Angioplasty
- IA vasodilators
Definitions of Vasospasm

- Radiographic (RVS)
  - Radiologic detection of narrowing, e.g. angiography
    - Arterial narrowing, slowing or increased transit time of blood/contrast
    - Incidence 30-70% (67% Dorsch et al)

- TCDs
  - Mild 120-200 cm/s, consistent with ~50% narrowing MCA (Aaslid ‘84);
  - Severe >200 consistent with >50% reduction luminal diameter
  - Lindegaard: Distinguishing VS from hyperemia
    - Helps to increasing TCDs due to VS from increases due to changes in cerebral blood flow
    - Vmca:Vica, <3 NI, 3-6 mild, >6 severe
Definitions of Vasospasm

- Symptomatic/Clinical/DIND/DCI
  - Decreased LOC w/focal neurologic deficit
    - ACA syndrome – Predominant frontal lobe findings w/abulia, urinary incontinence, drowsiness, slowness, delayed responses, confusion, whispering, grasp/suck reflex.
    - MCA syndrome – Hemiparesis, monoparesis, aphasia
    - CAUTION: R/O other causes of delayed deterioration after SAH
  - Incidence ~1/3 (Cooperative 28%, Tirilazid 30%)
Risk factors

- Clinical grade (e.g. Hunt Hess) c/w risk of CVS while blood volume (e.g. Fischer grade) c/w severity of CVS
- Blood clots near proximal extent major IC vessels
- Tobacco, cocaine
- Elderly? Not according to Torbey, Rabb, Charpentier, Dewey
- Location of aneurysm???
Pathophysiology

- Cerebral arterial wall:
  - Medial thickening
  - Corrugation of IEL and intima
  - Endothelial vacuolization
  - Loss of tight junctions
  - Breakage of IEL
  - Medial myonecrosis
Pathophysiology

- “Spasmogens” – thought to be released by lysis of RBCs, oxyhemoglobin induced free radicals
- Endothelin – vasoconstrictor autocoid
- NO deficit – antagonist of ET; inactivated by oxyHgb
- Eicosanoids – PGs & LTs
  - Some PGs are vasoactive
  - Disruption in balance of PGs and LTs
- Inflammatory cascade
Treatment and prevention of vasospasm

- Early obliteration and clot removal
- Reduce ICP – EVD/LD, clot evacuation
- Euvolumia to hypervolemia/HHH
- Reduction of seizures/AEDs
- Corticosteroids
- Angioplasty
- Papaverine/IA vasodilators
- Statins
- Mg
- ET antagonists
- IA ballon pump
Classification and Evidence of Therapeutic Effectiveness

- Class I – Evidence from one or more well-designed, randomized, controlled clinical trials, including overviews of such trials
- Class II – Evidence from one or more well-designed comparative clinical studies, such as nonrandomized cohort studies, case-control studies, and other comparable studies
- Class III – Evidence from case series, comparative studies with historical controls, case reports and expert opinion

Bullock, et al. Guidelines for the Surgical Mgmt TBI; Neurosurgery 3/06
Early obliteration and clot removal

- Securing aneurysm early permits aggressive early treatment of VS
- Surgery allows clot removal which may reduce incidence of VS
  - Mizukami, Case series(III) 1982
    - “...no spasm or only mild spasm in any site where the blood clot had been successfully removed. Delayed neuro deficits occurred only in those cases in which subarachnoid blood clot remained in the cisterns. These results suggest that it is possible to prevent intracranial spasm and associated neurological deterioration by early operation and removal of clotted blood.”
  - Ohta, Case series(III) 1982
    - “Extensive clot evacuation within 48 hrs after the onset did not prevent the development of VS but reduced the severity of VS”
Early obliteration and clot removal

- **Intracisternal TPA**
  - **Findlay 1995**
    - Double-blind, placebo controlled (I)
    - Single intracisternal dose after clipping
    - Good outcome in 57% vs 43% @ 3 mos
    - Not statistically significant
  - **Sasaki 2000**
    - Case series, 28 surgical pts (III)
    - Cisternal irrigation with urokinase
    - In the 120-IU/mL group, no symptomatic vasospasm occurred
Early obliteration and clot removal

Hamada 2000

- Case series(III), 15 pts
- Intracisternal UK after GDC
- “Although 1 pt developed a transient neuro deficit, no patients manifested permanent delayed neurological deficits as a result of vasospasm

Hamada 2003

- Prospective, randomized(I), 110 pts
- GDC followed by IT urokinase infusion into the cisterna magna
- Symptomatic VS occurred in 5 pts with and 16 w/o ITUKI therapy; the difference was significant (P=0.012).
- Although the mortality rate did not differ between the groups, ITUKI therapy had significantly better outcomes than those without (P=0.036)
Early obliteration and clot removal

- Amin-Hanjani 2004
  - Rvw, meta-analysis, all controlled trials included (I)
  - 652 pts
    - Absolute RR of 14.4% ($P < 0.001$) for DIND
    - Absolute RR 9.5% ($P < 0.01$) for poor GOS
    - Absolute RR 4.5% ($P < 0.05$) for death
    - Effects did not differ on the basis of the type of thrombolytic agent used (tpa vs urokinase) or method (intraop vs postop)
    - Studies that enrolled only patients at high risk for vasospasm seemed to demonstrate greater tx effects
    - Analysis limited by the predominance of nonrandomized studies (?Level I)
Reduce ICP – EVD/LD

- Hasan 1989
  - Case series(III), 473 pts, 91 w/HCP
  - Almost half of patients w/acute HCP and impaired consciousness improve spontaneously
  - 26/66(40%) w/HCP and altered MS improved spontaneously w/in 24 hrs

- Ventriculostomy often improves presenting grade and opportunity to treat
  - Hasan 1989 (series as above)
  - Rajshekhar 1992
    - Retrospective rvw(III), 194 pts, 52 developed HCP
    - 26/52 improved w/EVD
  - Mehta 1996
    - Retrospective rvw(III)
    - 32/105 pts w/HCP
    - 37% of pts w/HCP improved w/EVD
Reduce ICP – EVD/LD

◆ Suzuki 2000
   - Series(III), 103 Grade IV and V Hunt and Hess pts
   - Statistically significant neurologic improvement seen

◆ Klimo 2004
   - Retrospective rvw(III), 81 pts
   - Statistically significant reduction of clinical vasospasm, need for angioplasty and incidence of vasospastic infarction

◆ Fountas 2006
   - Literature review of 8 series examining EVD in SAH
   - Conclusion: “significant variability and heterogeneity in reported series…insertion of an EVD in pts with aHCP secondary to aSAH, particularly in patients of poor clinical grade is a necessity”
CCBs

- Barker and Ogilvy, 1996
  - Metaanalysis of all published randomized trials of nimodipine
  - 7 trials, 1202 pts
  - Ntop improved outcome according to all measures examined – odds of good and good+fair outcomes, deficit, mortality, CT-infarction rate
CCBs

- Cochrane rvw 2005
  - All randomized trials (1)
  - 12 trials, 2844 pts
  - Ntop 8/1574
  - Nicardipine 2/954
  - AT877 (rho kinase inhibitor) 1/276
  - Mg 1/40
  - Overall reduced poor outcomes & 2° ischemia, mostly due to Ntop
  - RR of poor outcome 0.82; Ntop alone is 0.7!
  - NNT to prevent single poor outcome = 20
Corticosteroids

- Cochrane rvw, 2005
  - All randomized, placebo controlled trials of corticosteroid therapy(I)
  - 3 trials, 256 pts
  - Studies differed substantially w/regard to populations, drugs & methodological quality
  - No. of pts was too small to make definitive conclusions, no evidence of beneficial or adverse effect
Corticosteroids

- U74006F, AKA tirilazad; 21-amino steroid
- Max beneficial effects of steroids e.g. antioxidant, eliminate glucocorticoid side effects
- Dorsch, 2001
  - Metaanalysis of 4 randomized, placebo-controlled studies (I)
  - 3500 pts
  - Trend toward efficacy to reduce mortality in poor-grade men
  - Not for use in U.S.
HHH

- Kosnick, Hunt ‘76
  - Series(III), 7 pts
  - Reversal of ischemic sx in 6/7 pts w/vasopressors & hypervolemia

- Kassell 1982
  - Case series(III), 58 pts w/agram confirmed VS
  - Intravascular volume expansion and induced hypertension are effective in reversing ischemic deficits from vasospasm

- Awad 1986
  - Case series(III), 39 pts w/clinical vasospasm w/agram verification
  - Early surgery + HHH tx
  - Death or major neuro deficit of 7% w/HHH was comparatively low vs. recent reports
1994 Position paper

- Stroke Council, AHA
- Despite the recognition of NO prospective, randomized, controlled trials:
  “HTN/hypervolemia/hemodilution are recommended for the PREVENTION and TREATMENT of ischemic complications from vasospasm.”
Cochrane review 2004 – 28 yrs since Kosnick and Hunt!

- Rvw of ALL randomized controlled trials of vol expansion(I)
- Only 3 studies found, of which only 2 truly randomized controlled, with very small numbers
- “no sound evidence for the use of vol expansion therapy”
Angioplasty

- Angioplasty
  - No randomized, controlled trials
  - Zubkhov ’84
    - Series(III)
    - Aplasty 105 vessels in 33 pts
    - No recurrence of spasm after balloon dilatation
  - 4 case series(III) - Bejjani ’98, Coyne ’94, Eskridge ’90, McDonald ’95)
    - Neurologic improvement in 31-80% of pts
IA delivery of vasodilators

- Intraarterial vasodilators
  - Transient
  - Papaverine - Usefulness limited by side effects, such as neurotoxicity, increased ICP, rebound VS
  - Biondi ’04, Badjatia ’04
    - 2 retrospective reviews of IA CCBs
    - Clinical improvement & angiographic dilatation seen; increased ICPs
IA delivery of vasodilators

- Hoh 2004
  - Review of clinical series
  - Papaverine
    - clinical improvement in 43% of patients only transiently, requiring multiple tx
    - significantly improved mean TCD velocities but only for <48 hrs
    - improved CBF in 60% but only for <12 hrs
    - Associated with increases in ICP
  - Nicardipine
    - clinical improvement 42%
    - significantly improved mean TCD velocities lasted 4 days
    - NO COMPLICATIONS
ET antagonists

- Shaw 2000
  - Randomized, blind placebo-controlled trial of TAK-044, $\text{ET}_{\text{A/B}} \text{R}$ antagonist(I)
  - 420 pts
  - Trend to reduced ischemic events but no significant diff in overall outcome or mortality
ET antagonists

Vajkoczy 2005

- Randomized, double-blind placebo-controlled trial of clazosentan, selective ETₐ R antagonist(I)
- 32 pts
- Reduced I of angiographic VS and reversed VS in pts initially treated w/placebo
- Lower incidence of infarctions in tx group
Statins

- Modulate endothelial fx by reducing vascular inflammation, inhibit vascular smooth m. proliferation, decrease plt aggregation, promote NO-mediated vasodilatation (Davignon ’04)
- Singhal 2005
  - Retrospective rvw(III)
  - Increased risk of VS w/statins
- Parra 2005
  - Retrospective rvw, 60 pts(III)
  - Significantly lower rate of DIND
Statins

- Tseng 2005
  - 80 pts randomized (I)
  - Reduced DIND and mortality

- Lynch 2005
  - Randomized, placebo controlled (I)
  - 19 in tx arm
  - Decrease in DIND and radiographic VS
IA balloon pump

- May be a consideration in pts with cardiac failure and poor cardiac function to augment cerebral perfusion in place of HHH therapy
- Apostoloides 1996
  - Case series(III), 2 pts
- Nussbaum 1998
  - Case report
- Rosen 2000
  - Case series(III), 2 pts
- Span 2001
  - Case series(III), 6 pts
- Sato 2001
  - Case series(III), 2 pts
Summary

- Vasospasm continues to adversely affect a significant proportion of aSAH population
- Many “tried and true” methods of prevention/reversal of VS are not based on strong evidence
- There is a need for more critical, evidence-based evaluation of new and existing treatments