ANTICOAGULATION AND THE EYE

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Disclosure Statement:
Nothing to disclose
Case History

• 78 year old Caucasian male
• Consult for eye exam
• Chief complaint:
  • Broke glasses when fell onto his face and hit right side of head 8 days ago
    • Got black right eye & vision fuzzy OD
  • Did not go to ED or see PCP since incident
• POHx: non-contributory
Case History

• PMHx:
  • Atrial fibrillation
  • Peripheral vascular disease

• Meds:
  • **Dabigatran** 150mg PO every day
Pertinent Exam Results

• BCVA: OD 20/30 (essentially stable); OS 20/20
• Pupils: PERRL, no APD
• EOMs: No restrictions, no pain, no diplopia
• CF: FTFC OD, OS
• External: Mild ecchymosis around OD; healing abrasion on forehead; no pain or step-offs with orbital rim palpation
• SLE: Unremarkable OU
• IOP: OD/OS 15 mmHg
• DFE: No heme, breaks, RD
CT of Head

Findings:
Relatively hypodense bilateral subdural fluid collections
Diagnosis & Plan

• Chronic subdural hematoma due to minor head trauma (MHT) after fall
  • Long term use of anti-coagulants (dabigatran)
• No ocular sequelae

• Consult with neurosurgery
  • Monitor, repeat CT of head
  • Go to ED for HA, diplopia or other visual changes
Higher risk of intracranial injury when anti-coagulated

• Common practice to image patients after MHT
  • EDs have protocols in place for immediate management as well for observational periods
Conclusion:
If negative initial head CT, recommend 24-hr observation period followed by second CT
General Indications for Anticoagulation
Venous Thromboembolism

- Deep Venous Thrombosis
- Pulmonary Embolism
Atrial Fibrillation (AF)

• Thromboembolic complications
• Associated with cardiac valve replacement
Post-Myocardial Infarction

• Reduce risk of:

  Recurrent MI  CVA  Systemic embolism  Death
Coumadin (warfarin)
Inhibits Vitamin K-dependent Coagulation Factors
Clinical Risk Factors for Major Bleeding (%)

- Systolic BP > 160 mmHg: 10%
- Kidney failure: 5.9%
- Stroke: 5.3%
- Prior major bleeding: 12.1%
- Age > 65 y/o: 53.3%
- Antiplatelet agent: 1.7%
Beware: Drugs & Dietary Changes!
Dosage & Administration

American College of Chest Physicians evidence-based clinical practice guidelines

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<th>Day</th>
<th>INR</th>
<th>Dose (mg)</th>
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<td>Day 1-3</td>
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<td>4</td>
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<td>Day 4</td>
<td>&lt;1.3</td>
<td>5</td>
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<td>1.3 to &lt;1.5</td>
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<td>1.9 to &lt;2.5</td>
<td>1</td>
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<td>&gt;2.5</td>
<td>None until &lt;2.5</td>
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Loading Dose Schedule for Warfarin Initiation

Routes of administration:

IV versus Oral
Dosage & Administration

Monitoring: narrow therapeutic range
Direct Oral Anticoagulants
Pradaxa (dabigatran)

- FDA approved Oct 2010
- Reduce risk of CVA & embolism in atrial fibrillation
Xarelto (rivaroxaban)

• Reduce risk of CVA & embolism in AF
  • FDA approved November 2011
  • Approved earlier to lower the risk of DVT after hip & knee replacements

• November 2012: also approved to treat DVT & PE; reduction of risk of recurrence
Eliquis (apixaban)

- FDA approved
  - Dec 2012
- Reduce risk of CVA & embolism in AF
Savaysa (edoxaban)

• FDA approved factor Xa inhibitor for:
  • Prevention of CVA & non-central-nervous-system embolism in patients with nonvalvular atrial fibrillation
  • DVT & PE
Antiplatelets
Aspirin

40-50 million Americans use for MI prevention

81 versus 325 mg

General mechanism of action
Plavix (clopidogrel)

• FDA approved Nov 1997
  • Indications: acute coronary syndrome; recent MI/CVA or established peripheral arterial disease
  • DAPT Trial results
  • 30 million prescriptions
    in 2009
DAPT Trial Results

• Plavix/Effient + ASA vs ASA alone
• ↓risk of stent thrombosis & cardio- & cerebro-vascular events
• Greater bleeding risk & increased death greater in dual group
• FDA: Benefits of Plavix/Effient cont to outweigh potential risks
  • Pts should cont to take drugs as directed to prevent ischemic events
  • Health care providers should not change how they prescribe drugs
Ocular Complications of Anticoagulants / Antiplatelets
Case 1
Case History

• 61 year old Caucasian male (new patient)
• Urgent referral from ER
• Chief complaint: left eye irritation and blurry vision starting this morning. 6/10 eye pain
  • Rubbed eye and noticed blood in eye
  • Denies valsalva/trauma but bruises easily
  • Occasional horizontal diplopia in extreme right gaze only; no diplopia in primary gaze
• POHx: unremarkable
<table>
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<tr>
<th>Pertinent Medical History</th>
<th>Medications</th>
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<tr>
<td>Myocardial infarction</td>
<td>Plavix 75mg</td>
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<tr>
<td>Peripheral vascular disease (pulmonary embolism)</td>
<td>Warfarin (added 2.5 months after Plavix) 5mg tab every evening except 1.5 tabs Tuesday, Thursday, Saturday</td>
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<tr>
<td></td>
<td>INR was 3.6; Today: 2.8</td>
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<tr>
<td>HTN</td>
<td>Hydrochlorothiazide</td>
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Pertinent Exam Results

• BCVA: OD 20/20; OS 20/25
• Pupils: PERRL; (-) APD
• EOMs: Full OU; no restrictions but mild pain on eye movement
• CT: Ortho
• CF: FTFC OD/OS
• SLE: OU NSC
• Ta: OD/OS 20 mmHg
Sub-Conjunctival Hemorrhage 360°
Significant elevation over limbus and lid & ecchymosis
Left periorbital soft tissue swelling w/o evidence of post septal extention or retro-orbital hematoma
3 Week Follow Up Visit

OD
Sub-conjunctival hemorrhage 2 days after last exam which as since resolved

OS
Significantly improved!
Diagnosis & Plan

• Anticoagulation Clinic informed of findings
• Seek eye care annually
• Incidence of subconjunctival hemorrhages related to long term AC use: 1.5-5%

• Risk **twice** as great in older patients on AC therapy than younger patients\(^1\)\(^-\)\(^2\)

• Bleeding **3x** as common if INR 3.0-4.5 vs in patients with INR 2-3\(^3\)
Case 2
Case History

• 69 year old Caucasian male

• Baseline eye exam
  • Triage call for urgent exam for ‘blurry vision’ OU

• Chief complaint
  • Vision blurred and ‘distorted’ OU x 3 months. Unsure if worse or not since onset but difficulty reading street signs and newspaper with current spectacles.

• POHx:
  • Broken blood vessel OS X ~2000 and has to turn eye to see better (poor historian)
Pertinent Medical History

• Atrial fibrillation
  • Warfarin: 2.5mg tablet
    • 2 tablets every evening except 1 Sun, Tues & Thurs
    • Last INR: 2.6 2wks
    • INR range: 1.3-2.8 over past year
  • Aspirin 81mg

• Congestive heart failure
  • Amiodarone
  • Hyperlipidemia
    • Pravastatin
  • HTN
    • Metoprolol
  • No DM
Pertinent Exam Results

• BCVA: OD 20/25; OS 20/30
• Pupils: PERRL; (-) APD
• EOMs: Full OU
• CF: FTFC OD/OS
• SLE: OU 2+NSC, TR PSC
• Ta: OD/OS 20 mmHg
Dilated Fundus Exam

- Retinal heme inf arcade
- Old BRAO superior
OD  Focal hyper-reflectivity of inner retinal layer obscuring underlying structures sup/nasal to fovea

OCT Cirrus Macular Cube & 5-line HD Raster
OS

Generalized thinning sup/ nasal macula  
c/w old  BRAO
2 Month Follow Up: OD
2 Month Follow Up: OS
Diagnosis & Plan

• Continue to periodically monitor retinal hemorrhages
• Inform Anticoagulation Clinic

• Ordered Carotid Doppler Ultrasound after initial exam due to BRAO OS
  • Less than 50% stenosis of right & left internal carotid arteries
Discussion

• Beaver Dam Study
  • Retinal hemes 3x more prevalent in AC patients vs non-AC patients (4.5% vs 1.5%)\(^1\)
    • Non-diabetics
    • ≥65 years old
    • ≥75 years old, then 9.5x more likely to have hemorrhages

• Framingham Eye Study
  • 0.9% of eyes had retinal hemes\(^2\)
Ocular Hemorrhage with Warfarin, Superstein et al, *CJO* 2000

- Risks for retinal hemes
  - Pre-existing ocular disease
    - i.e., retinal vascular disease in fellow eye
  - Hypertension
  - Longer duration, more intense AC, use of concurrent meds
  - Increased age
    - Twice as great in older vs younger patients
Case 3
Case History

• 66 yo Caucasian male
• Self made appointment for exam
• Chief complaint:
  • Progressively blurry vision OD x 3 days to the point he can only see outlines and light. Noticed a floater/squiggle a few weeks prior
  • Went to local ER 3 days ago and referred to OMD
    • Told he had ‘bleeding in his eye’
    • Would like to transfer care to VA & 2nd opinion
    • Self d/c Plavix x 3 days ago
Case History

• POHx: non-contributory

• PMHx:
  • CVA vs TIA vs anxiety episode
  • HTN
  • No DM

• Meds:
  • ASA 81mg daily
  • Plavix until 3 days ago
Pertinent Exam Results

• BCVA: OD HM @ 8 feet
   OS 20/25
• Pupils: ERRL; (-) APD
• EOMs: Full OU
• CF: FTFC OD, OS
• SLE: OD/OS 2+ NSC, ACC
• Ta: OD 15 / OS 12
Vitreous Hemorrhage → Weiss Ring

B-scan:
Mild vitreous opacity w/ good after-movement

DFE:
PVD, mild preretinal opacity; no tears or detachments
Diagnosis & Plan

• Hemorrhagic PVD OD
  • Plavix discontinued by prescriber 10 days after initial exam after latest stress test results

• RTC 2 weeks or ASAP if any symptoms of RD
  • Patient educated blood will likely self-resolve
  • Patient educated to avoid heavy lifting & bending over; sleep upright as possible
Discussion

• Conclusion:
  • “Patients taking ASA, clopidogrel, or warfarin who develop an acute PVD are more likely to present with VH.”
Discussion

• AC/APs generally do not cause VH but may enhance bleeding
  • Early Treatment of Diabetic Retinopathy Study
    • Did not show increased risk of VH among aspirin users

…risk of heme maybe elevated during transition period when patients are switched from AC to rivaroxaban…
Intraocular Hemorrhage and Novel Oral Anticoagulants

- *JAMA Ophthalmol* July 2015
  - New oral anticoagulants “…do NOT increase the risk of substantial intraocular bleeding compared to warfarin/Coumadin/heparin.”
  - Rate of serious bleeding events was VERY low <0.4%! 
Case 4
Case History

• 66 y/o WM
• Urgent request for exam
• Chief complaint
  • Transient blurry vision OD x 3+ months
  • Blur lasts a few days then resolves
• PMHx: DM2, HTN
  • Samter’s Syndrome
• Meds: Glyburide, Metformin, Lisinopril
  • 1.3grams ASA daily
Ocular History

• CE/PCIOL OU
  • Dislocated IOL OD; surgically retrieved & iris-fixated

• Macular hole OD s/p PPV & gas bubble
  • Subsequent RD s/p SB & cryotherapy
Pertinent Exam Results

- **BCVA**: OD 20/60 EV; OS 20/20
- **Pupils**: (3->2, 4->3)RRL, (-)APD
- **SLE OD**: see next slide
  - PCIOL decentered inferior w/ sutures at 2:00 & 8:00
- **IOP**: OD 45, OS 24
- **Gonio**: Open; no hyphema but hazy view inferior
- **DFE**: Diffuse ant vit heme; no retinal break
Anterior Segment Findings
3+ swirling RBCs, pigment on inf endo, iridodonesis
B-scan: Diffuse anterior vitreous hemorrhage
Diagnosis & Plan

• Iris-sutured IOL induced Uveitis-Glaucoma-Hyphema+VH (UGH+) complicated by high dose ASA
  • Start IOP lowering medications
  • Rec’d sleeping w/ head elevated
  • Retina consult: No surgical intervention; CPM
• 2 month follow up visit
  • No changes per pt, notes ‘rebleeds’ occasionally
  • ASA d/c’d due to ineffectively
Discussion

• UGH+
  • Hyphemas reported in patient w/ pre-existing conditions such as iris-fixed IOLs

• Samter’s Syndrome
  • Inflammatory disease of respiratory mucosa
  • Clinical triad:
    • Asthma, ASA sensitivity, nasal/ethmoidal polyposis
  • Tx: ASA desensitization
    • Initially ‘challenged’ w/↑ doses (650-1300mg/day)
Other ocular Hemorrhages
Retina

Sub-sensory    Sub-hyaloid
Significant association between ASA & ODH
Possible association between ODH & generalized vascular disease
Latest study findings
The European Eye Study 2012

Frequent ASA use associated w/ early & wet late AMD
ASA, clopidogrel & warfarin significantly associated with increased risk of intraocular hemorrhage in wet AMD
✅ Regular ASA use 10 years prior associated with small but statistically significant increase in incident late and wet AMD
Blue Mountains Eye Study

ASA use associated with 2-fold increase in wet AMD during 15-year period
Higher incidence of central geographic atrophy weakly associated with ASA use
Large-scale randomized trial with 10 years of treatment and follow-up, low-dose ASA had no large beneficial or harmful effect on risk of AMD
“We strongly recommend that AMD patients should be on aspirin if it is recommended by their primary physician”
*Most retinal or subretinal hemorrhages < 1DD

**No association of AC/AP use with hemorrhage except in participants with HTN
No change to clinical recommendations

Insufficient evidence for patients with AMD to stop ASA if clinically warranted for secondary prevention of cardiovascular disease
Prescribing of Supplements

- AREDs recommended supplements for AMD
- Vitamin E
  - May ↑ anticoagulation effect (↑INR)

Because of warfarin’s narrow therapeutic index, AC status should be carefully monitored with use of supplements since serious reactions associated w/ small changes in INR

Recommendation:
Evaluate warfarin response when vitamin E used in combination
Prescribing of Supplements

- Increased AC effect (↑INR) & AP activity
- Decreased AC effect (↓INR)
AC & Ophthalmic Surgery

• Overall, very low risk of hemorrhaging
• Cataract
  • No difference w/ or w/o warfarin use prior to surgery\(^1\)
  • **Safe with uncomplicated phacoemulsification**\(^2\)
  • Significant increase in minor complications
    • Sharp needle & anesthesia related complications\(^3\)
• If ECCE, stop 1 week prior
AC & Ophthalmic Surgery

Glaucoma
• Statistically significant ↑ in hemorrhagic complications\(^1\)
  • Patients on AC had significantly higher complication rate than those on AP or no treatment\(^1\)

Oculoplastics
• Little data available
• Half of surgeons polled stop warfarin
• Local specialist: stop 1 week prior
AC & Ophthalmic Surgery

• Vitreo-Retinal
  • Most hemorrhagic complications due to manipulation of retina
  • May stop warfarin if thromboembolic risk low\(^1\)
  • No intraoperative complications\(^2\)
    • Maintain therapeutic levels of AC during surgery
  • Intravitreal injections
    • No hemorrhagic events; can continue AC safely\(^3\)
Pre-cautions & Other Potential Complications
Pre-cautions & Other Potential Complications

- Bleeding
- Tissue necrosis
Pre-cautions & Other Potential Complications

• Systemic atheroemboli
  • Microemboli to the feet: “Purple Toe”

• Heparin-induced thrombocytopenia
Pre-cautions & Other Potential Complications

- Pregnancy category D
  - If mechanical heart valves otherwise Category X
  - Risk of
    - Warfarin embryopathy (including optic atrophy)
    - Fetal hemorrhage & mortality
- Reproductive potential
  - Discuss pregnancy planning & potential risks to fetus
- Nursing mother
  - Warfarin not detected in human milk
Pre-cautions & Other Potential Complications

• Renal impairment
  • No dosage adjustment necessary

• Hepatic impairment
  • Can increase effectiveness of response through
    • Decreased production of clotting factors
    • Decreased warfarin metabolism
Pre-cautions & Other Potential Complications

• Pediatric use
  • Avoid activity or sport that may cause traumatic injury
  • Dosing varies by age
  • Target INR difficult to achieve/maintain so more frequent testing

• Geriatric use
  • ≥60 yo have >expected INR response
  • Contraindicated in unsupervised patients w/ dementia
  • Consider low initiation and maintenance doses
AC/AP in Primary Eye Care
Ocular Ischemic Syndrome
Ocular Ischemic Syndrome

• Maybe initial manifestation of carotid occlusive disease in ~70% of patients

• Often have systemic vascular diseases related to atherosclerosis
  • Ischemic heart disease, previous CVA
  • Peripheral vascular disease (DVT)

• Average stroke rate reported to be significantly higher in patients w/ OIS (4% per year) vs 0.49% per year in controls
• **Antiplatelets: mainstay of medical therapy**
  
  • **Symptomatic**
    - Prompt A/P therapy to prevent recurrent TIA
    - ASA vs ASA & clopidogrel
    - A/C not indicated
  
  • **Asymptomatic**
    - ASA only [unless other concomitant condition(s)]
Hollenhorst Plaque/Embolus
Conclusion: Asymptomatic retinal cholesterol embolism is an important risk factor for cerebral infarction...
Retinal Vascular Occlusions

CRAO: “ocular analogue of cerebral stroke”

Often are undiagnosed systemic vascular risk factor & @ hi risk of systemic ischemic event such as CVA

Event rates for MI similar w/ RVO vs controls; event rate of CVA almost 2-fold vs controls
AC/AP in Primary Eye Care

- Transient visual obscurations (amaurosis fugax)
  - Highlighted in new definition of TIA
  - Greatest risk of stroke (& MI) within 1st few days of event
Conclusion / Clinical Pearls

• Be familiar w/traditional & newer AC/AP therapies
  • Importance of review of medications, ROS
• AC/AP can affect eye health, ocular surgery, prescription of supplements
  • Routine exams/follow-ups not recommended
• Maybe prescribed as a result of an ocular disease which maybe 1st presenting sign for need for AC/AP therapy
• Know potential non-ocular complications of AC/AP therapy such as head trauma
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