E·QUAL | EMERGENCY QUALITY NETWORK

Blood Pressure Management in ICH

Latha Ganti

American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

Presenter

Latha Ganti, MD, MS, MBA, FACEP, FAHA
Professor of Emergency Medicine & Neurology
University of Central Florida College of Medicine

Disclosures

- NONE

UCF | Emergency Medicine
UNIVERSITY OF CENTRAL FLORIDA

Envision
PHYSICIAN SERVICES

Role of BP in ICH

- Relationship between BP and outcome not straightforward
- Intuitively, high BP would seem to worsen the ”force” behind the bleeding, resulting in hematoma expansion
- But we also know that many pts with hypertension “live” at high BPs, so maybe they need that pressure for perfusion
- Is brain autoregulation maintained at very high pressures?
- If I lower BP, will I:
  - Cause perihematomal ischemia?
  - Reduce hematoma expansion?
  - Improve functional outcome?

E·QUAL | EMERGENCY QUALITY NETWORK

Will I cause perihematomal ischemia?

- ICH ADAPT RCT- n=75
  - Pts with spontaneous ICH <24 hrs after onset and sBP > 150 mm Hg randomized to IV antihypertensive Tx targeting sBP <150 mm Hg (n=39) or <180 mm Hg (n=36).
  - CT perfusion imaging 2 hours post-randomization.
  - Rapid BP lowering after a moderate volume of ICH does not reduce perihematoma CBF. These physiological data indicate that acute BP reduction does not precipitate cerebral ischemia in ICH patients.
- ICH ADAPT Observational sub-study n=20
  - Additional CT perfusion within 72 hours of ICH before and after BP Tx.
  - CBF remained stable after acute BP reduction, suggesting some preservation of cerebral autoregulation.
- Australian study n=21
  - MRI PWI and DWI in 21 ICH patients
  - MRI and CT images co-registered to ensure perfusion and diffusion changes were outside of the hematoma. Edema volumes measured on T2-weighted images. Apparent diffusion coefficient (ADC) values of the edematous regions were calculated.
  - Acute perihematomal oligemia occurs in acute ICH but is not associated with MRI markers of ischemia and is unrelated to edema formation.
  - Increased rates of water diffusion in the perihematomal region independently predict edema volume, suggesting the latter is plasma derived.

- →blood pressure lowering does not impair regional cerebral blood flow within the perihematomal region
- → perihematomal rim of low attenuation on CT appears to be caused by extravasated plasma and is not associated with MRI markers of ischemia

E·QUAL EMERGENCY QUALITY NETWORK

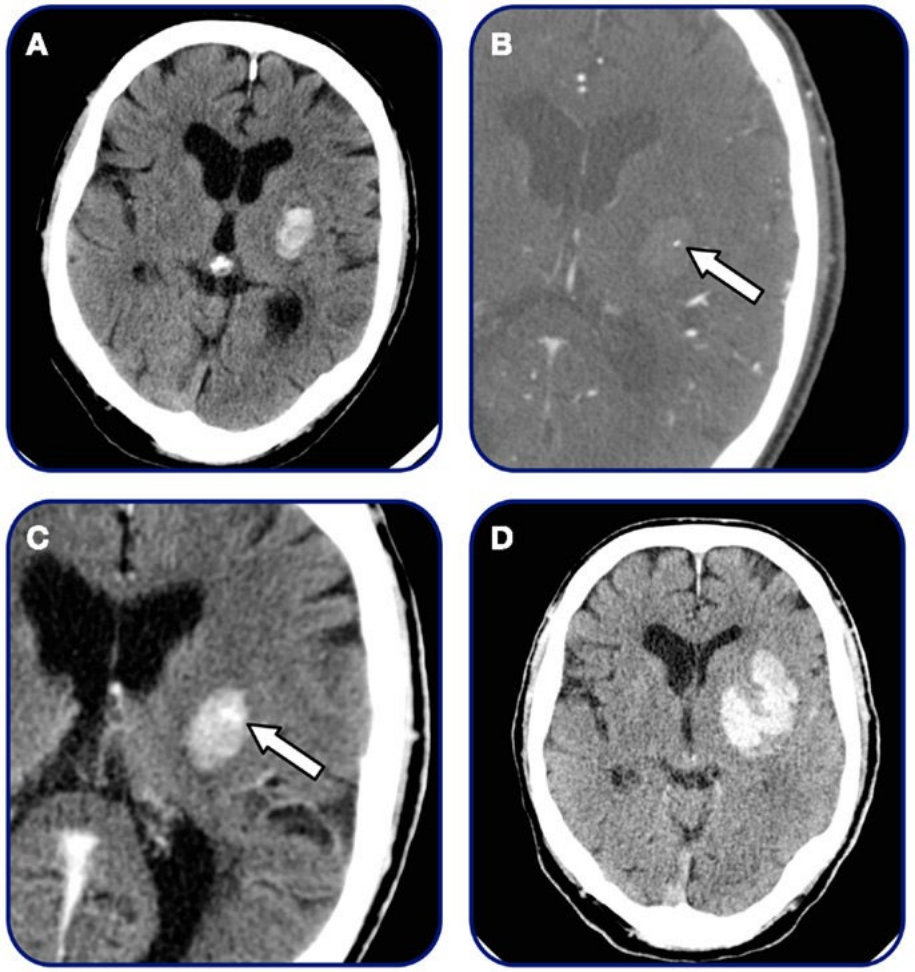
Hematoma expansion

- We know that risk of hematoma expansion is highest early in ICH course
- We know pts with hematoma expansion do worse (~10% expansion= 5% increase in mortality and 15% increase in Rankin 3-6)
- Hematoma expansion can be predicted by the spot sign

E·QUAL EMERGENCY QUALITY NETWORK

Spot sign

- **CT angiographic (CTA) spot sign** - defined as unifocal or multifocal contrast enhancement within an acute primary ICH
- Visible on CTA source images and discontinuous from adjacent normal or abnormal blood vessels
- Should NOT be present on pre-contrast images.
- Corresponds to a site of active, dynamic hemorrhage
- Present in about 30% of patients scanned within 6 hours of symptom onset



- Ovesen, Christian & Havsteen, Inger & Rosenbaum, Sverre & Christensen, Hanne. (2014). Prediction and Observation of Post-Admission Hematoma Expansion in Patients with Intracerebral Hemorrhage. Frontiers in neurology. 5. 186. 10.3389/fneur.2014.00186.

- *FIGURE- Spot sign and contrast extravasation. Patient admitted within 2 h after symptom onset. (A) Initial non-contrast CT demonstrating small basal-ganglia hemorrhage, (B) CTA source image demonstrating single spot sign (arrow), (C) 3-min post-contrast CT-imaging demonstrating contrast extravasation (arrow), and (D) 24 h follow-up CT revealing final hematoma volume.*

E·QUAL EMERGENCY QUALITY NETWORK

Prediction Score for Hematoma Expansion

Variable	Points
Warfarin sodium use	
No	0
Yes	2
Time to initial CT in hours	
<6	2
>6	0
Baseline ICH volume, mL	
<30	0
30-60	1
>60	2
CT angiography spot sign	
absent	0
present	3
unavailable	1
TOTAL	0-9

- Brouwers et al: JAMA Neurol 71:158, 2014

E·QUAL EMERGENCY QUALITY NETWORK

Performance of the Prediction Score for Hematoma Expansion and Mortality

- Brouwers et al: JAMA Neurol 71:158, 2014

Score	Expansion	In-hospital mortality
0	5.7%	2.9%
1	11.1%	13%
2	7.7%	14.8%
3	17.9%	23.5%
4	29.6%	33.3%
5	35.4%	34.1%
6	53.6%	75%
7	45.5%	45.5%
8	n/a	100%
9	80%	100%

Score 0	6%
Score 1-3	10%
Score 4-9	32%

E·QUAL | EMERGENCY QUALITY NETWORK

ICH ADAPT

Butcher et al, Stroke 2013

Will I reduce hematoma expansion?

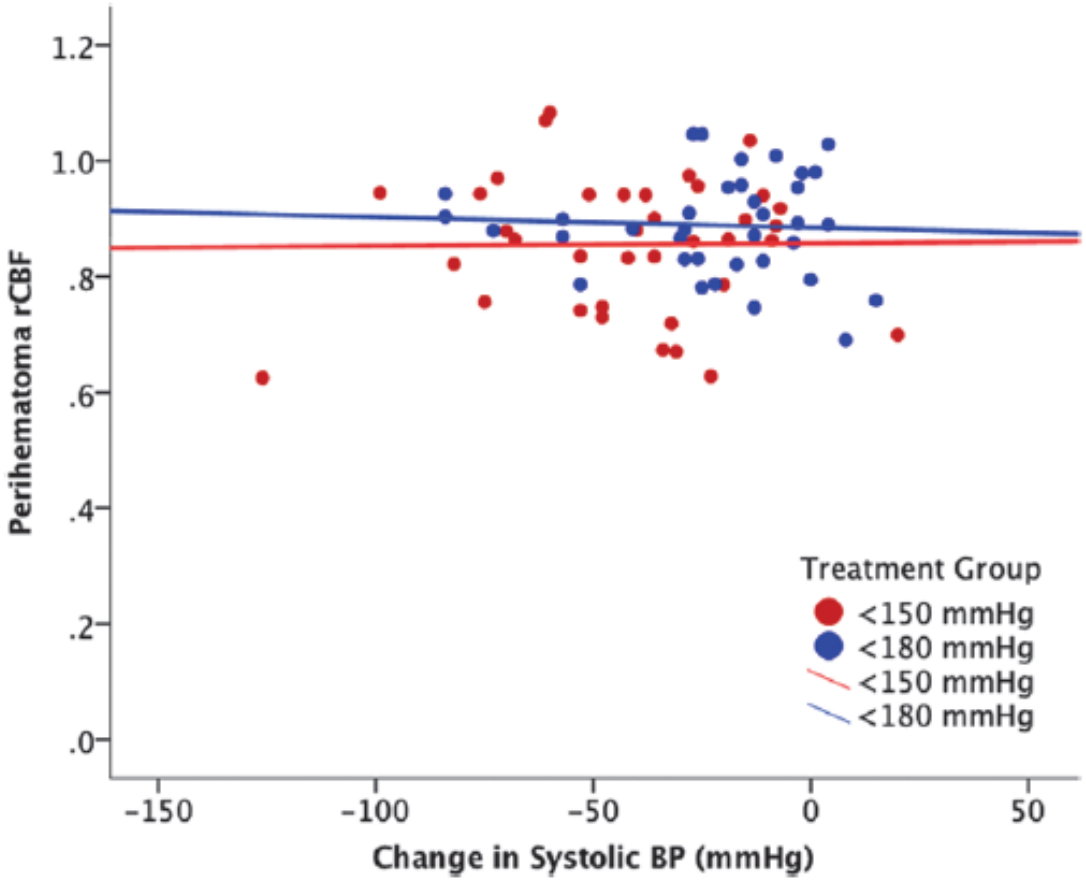


Figure 4. Linear regression indicated no relationship between the absolute change in systolic blood pressure (BP) and perihematoma relative cerebral blood flow (rCBF) in the <150 mm Hg (R=0.00005; 95% CI, –0.001 to 0.001) or <180 mm Hg target groups (R=0.000; 95% CI, –0.001 to 0.001). Confidence intervals removed for clarity.

→ No differences in hematoma expansion or clinical outcome

E·QUAL EMERGENCY QUALITY NETWORK

Anderson et al, 2013

Will I improve functional outcome or reduce death?

INTERACT 2 trial

- 2839 patients with ICH within 6 hours;
- Randomized to SBP<140 vs. SBP<180mmHg;
- Any BP medication was accepted
- Exclusions:
  - structural cerebral cause for ICH
  - Coma (GCS =3-5)
  - massive hematoma with poor prognosis
  - Planned early surgery to evacuate hematoma
- Primary outcome= death or bad Rankin (3-6)
- *Intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or severe disability.*

→ Aggressive lowering to <140 mmHg did NOT improve functional out come or reduce death

E·QUAL | EMERGENCY QUALITY NETWORK

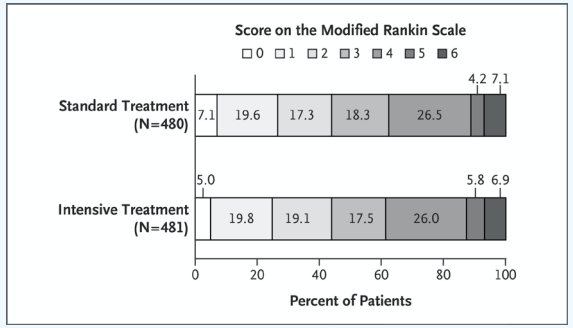
Quereshi et al., 2016

Will I improve functional outcome?

ATACH 2 trial

- 1000 patients with ICH within 4.5 hours; 56% Asian
- Randomized to SBP 110-139 vs. SBP 140-179 mmHg
- Nicardipine upto max dose then labetalol (US) or diltiazem/urapidil (outside US)
- Analysis adjusted for age, initial GCS, and presence of intraventricular hemorrhage
- Exclusions:
  - GCS < 5
  - ICH volume >60cc
- Primary outcome = Modified Rankin scale of 4-6 (death or disability) at 3 months after randomization
- Enrollment was stopped because of futility after the prespecified second interim analysis.

→Aggressive lowering to <140 mmHg did NOT improve functional outcome or reduce death



- rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment group than in the standard-treatment group

Question

What is the optimal blood pressure target in acute intracerebral hemorrhage?

1. 25% lower systolic BP than what patient presents with
2. 185/95 mmHg
3. Systolic 120-140 mmHg
4. Systolic 140-180 mmHg

AHA 2015 guideline recs

- **For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe *(Class I; Level of Evidence A*) and can be effective for improving functional outcome *(Class IIa; Level of Evidence B*).** (Revised from the previous guideline)

- **For ICH patients presenting with SBP >220 mm Hg**
  - **AHA: it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring *(Class IIb; Level of Evidence C*).** (New recommendation)
  - UpToDate: suggest aggressive reduction of blood pressure with a continuous intravenous infusion of antihypertensive medication and frequent (every five minutes) blood pressure monitoring. The optimal goal blood pressure is uncertain, but a SBP of 140 to 160 mmHg is a reasonable target.

E·QUAL | EMERGENCY QUALITY NETWORK

What drug should I use?

- Labetalol
- Nicardipine
- Clevidipine

OFF LABEL

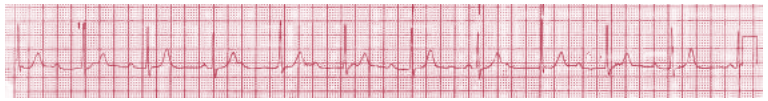
- Esmolol
- Diltiazem
- Nitroprusside
- Nitroglycerine
- Hydralazine
- Fenoldopam
- Enalaprilat

BOTTOM LINE

- Reduce BP to a target of 140-160 mmHg

Labetalol

- Mixed alpha and beta adrenergic blocker
- Fast onset (<5 min), lasts 2-4 hrs
- IV bolus dose: 20 mg initially, followed by 20 to 80 mg every 10 minutes to a total dose of 300 mg.
- Infusion dose: 0.5 to 2 mg/min
- Avoid in patients with
  - Asthma
  - COPD
  - Heart failure
  - Bradycardia
  - 2nd-3rd degree heart block



Nicardipine

- Calcium channel antagonist, with predominantly vasodilatory actions
- Onset of action= 1 - 2 min
- Half-life = 40 min
- Infusion dose: 0.5 to 1 mcg/kg/min, titrated to a max of 3 mcg/kg/min

Clevidipine

- Dihydropyridine calcium channel blocker
- Onset= 1-4 min
- Duration of effect= 5-15 min
- Infusion rate= 1 mg/hour, upto 21 mg/hour; titrate by 2.5 mg/hr q5–10min
- Contraindicated in patients with
  - severe aortic stenosis (because it increases the risk of severe hypotension)
  - disordered lipid metabolism (because it is administered in a lipid-laden emulsion
  - known allergies to soy or eggs (because these are used to produce the emulsion)

Question

Which of the following drugs is NOT indicated for blood pressure management in acute intracerebral hemorrhage?

1. Labetalol
2. Nicardipine
3. Clevidipine
4. Enalaprilat

Esmolol

- Off-label
- Cardioselective beta-1 receptor blocker
- Onset of action: 60 seconds
- Dosing:
  - Loading dose: 500 to 1000 mcg/kg over 1 minute (can be repeated once
  - infusion dose: 50 mcg/kg per minute until the max dose of 200 mcg/kg per minute is achieved
- Do not DC suddenly- start new med, titrate esmolol down, titrate new agent up
- No dose adjustment needed for renal or haptic impairment
- Contraindicated in patients with sinus bradycardia, sick sinus syndrome, atrioventricular heart block, heart failure, cardiogenic shock, pulmonary hypertension, and history of hypersensitivity reactions to esmolol.
- Do not give concurrently with Ca Channel Blocker (can precipitate hypotension and bradycardia)

Fenoldopam

- Dopamine (D1) receptor agonist; minimal adrenergic effects
  - results in decreased peripheral vascular resistance primarily in renal capillary beds, thus promoting increased renal blood flow, natriuresis, and diuresis. Fenoldopam has minimal adrenergic effects.
  - only intravenous agent that improves renal perfusion, may be useful in CKD pts
- Onset of action = 5-10 min
- Duration of action = 30-60 min
- Infusion Dose: 0.1 mcg/kg/min IV, titrated to max of 1.6 mcg/kg/min
- Caution in patients with glaucoma or increased ICP

Hydralazine

- Direct arteriolar vasodilator
- Onset of action: 10-20 min
- Duration: 4-6 hrs
- Dose: 10-20 mg IV bolus
- Adverse effects: sudden drop in BP, tachycardia, flushing, headache, vomiting, worsening angina
- Hydralazine not optimal due to longer onset and duration of action
- Not a preferred agent in patients with underlying coronary disease or aortic dissection, and a beta blocker should be given concurrently to minimize reflex sympathetic stimulation

Enalaprilat

- Inhibits angiotensin I to angiotensin II conversion via competitive inhibition of angiotensin-converting enzyme (ACE).
- Dose: 1.25 to 5mg every 6 hrs IV
- Onset of action = 15-30 min
- Duration of action= 6-12 hrs
- Used in acute left ventricular failure; too slow for most hypertensive emergencies
- Avoid in MI, renal insufficiency, and pregnancy

Questions ?

Thank You