BP management following non-traumatic intracerebral hemorrhage:

the Victoria General experience

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Objectives

- To outline the unresolved issue of blood pressure management following spontaneous intracerebral hemorrhage (sICH)
  - Summarize primary literature
  - Compare guideline statements
- To present the findings of our retrospective chart review conducted at Victoria General Hospital
- To solicit feedback from the group regarding knowledge translation of findings

Spontaneous intracerebral hemorrhage (sICH)

- Makes up ~ 15% of acute stroke cases
  - Least treatable form of stroke
  - Overall mortality > 40%

- Predictors of poor outcome in ICH:
  - Initial hematoma volume and location
  - Intraventricular extension
  - Hematoma growth

- ↑ BP may be a risk factors for hematoma expansion

Stroke 1997;28:2370-5.

Stroke 2004;35:1364-67.

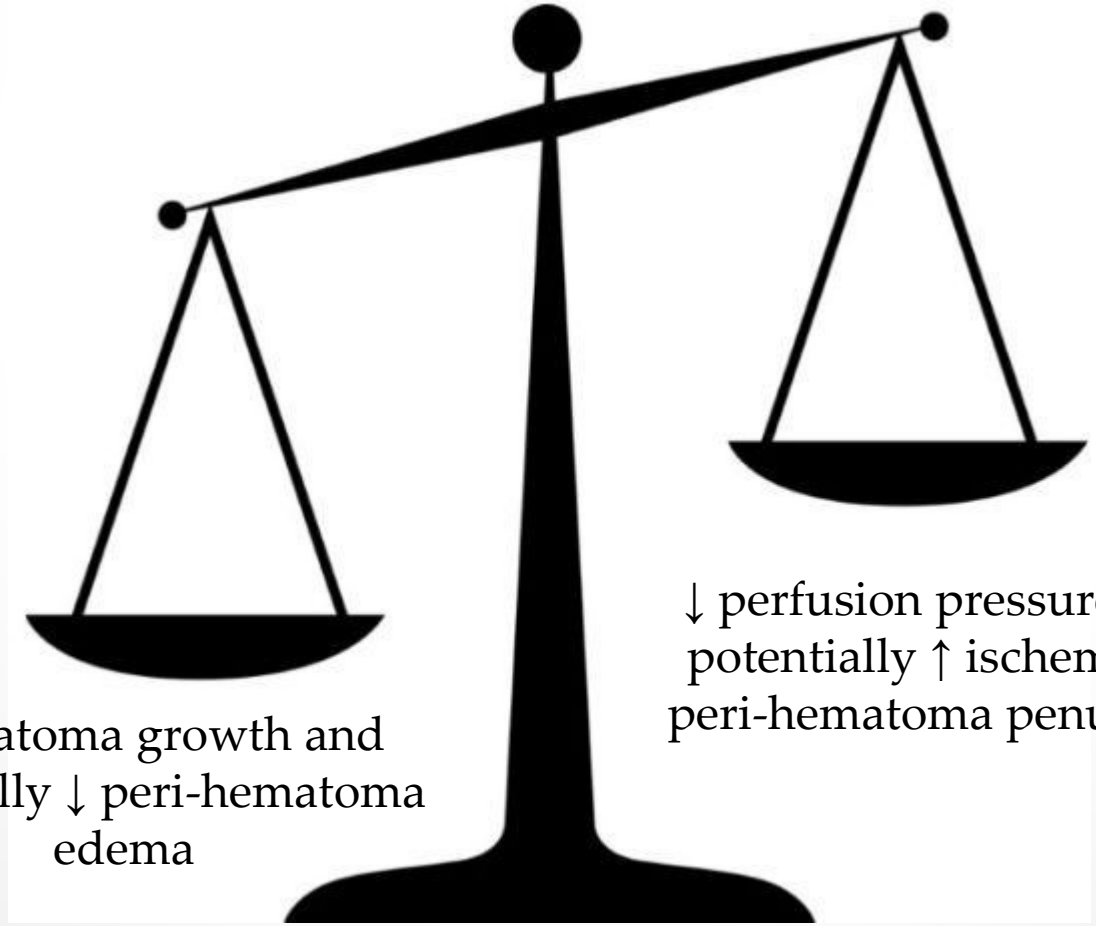
Blood pressure in sICH

- Elevated BP prevalent
  - Premorbid hypertension
  - Response to ↑ ICP to maintain cerebral blood flow (CBF)
  - Stress induced activation of neuroendocrine system
  - Damage to central autonomic centers
- Generally falls spontaneously within days
- Clinical significance conflicting:
  - ↑ mortality and disability
  - Contribution to hematoma expansion
  - Neurologic deterioration
  - ↑ risk of rebleeding

Cerebrovasc Dis 2017;43:207-13. Stroke and Vascular Neurology 2017;2:e000047

Blood pressure in sICH

- ↓ BP following ICH faces 2 conflicting processes



Early Guideline statements

- Recommend caution with early BP treatment
  - Potential precipitation of ischemic injury
- "If SBP > 180 mmHg – modest reduction to 160 mmHg" AHA 2010
- "A ↓ MAP >20% should be avoided"; "If SBP >180mmHg in known hypertensive, target SBP should be 170 mmHg" European Stroke Initiative 2006

Different process than ischemic stroke

- Ischemic stroke
  - Consistent U-shaped association between poor outcomes and SBP
  - Neurologic deficits & ischemia worsened by lower blood pressure
- Hemorrhagic stroke
  - Re-thinking peri-hematomal ischemic region
    - Hypoperfused area with no evidence of ischemia
    - Peri-hematoma CBF not ↓ by acute ↓ SBP
- Research question
  - If no risk of worsened ischemia, and potential for ↓ hematoma expansion, would aggressive bp management improve outcomes in sICH?

J Cereb Blood Flow Metab 2001;21:804-10. Stroke and Vascular Neurology 2017;2:e000047

Primary Literature

Trial	INTERACT-2 N Engl J Med 2013	ATACH-2 N Engl J Med 2016
Population	N = 2839 ICH < 6 hours SBP 150-220 mmHg	N = 1000 (stopped early for futility; goal N=1280) ICH < 4.5h SBP > 180 mmHg
Intervention	SBP < 140 mmHg w/in 1h and maintain x 7d SBP < 180 mmHg Any agent (IV or PO); d/c if < 130 mmHg	SBP 110-139 mmHg x 24h SBP 140-179 mmHg CIVI nicardipine then add labetalol; d/c if < 110
Outcomes & Results	Achieved mean SBP = **150 vs. 164 mmHg** % meeting target <140 SBP @ 1h = 33.4% (on average did achieve by 6 hrs) Death/major disability (mRS 3-6) @ 90d 52% vs. 55.6% (NS) Death 11.9 vs. 12.0% "shift" to favourable mRS OR 0.87 (0.77-1.00) p = 0.04 Significant improvement in HRQOL Hematoma expansion not significantly different (2.5 ml vs. 5.5 ml) Severe hypotension 0.5 vs. 0.6%	Mean SBP achieved at 2h = **128.9 vs. 141.1 mmHg** % meeting target SBP @ 2h = 87.8 vs. 99.2% Failure to maintain target = 15.6% vs. 1.4% Death/major disability (mRS 4-6) @ 90d 38.7 vs. 37.7% (NS) Death 6.6 vs. 6.8% No "shift" to favourable mRS No difference HRQOL Hematoma expansion > 33% 18.9 vs. 24.4% (NS) Hypotension 1.2 vs. 0.6% Renal adverse events 9 vs. 4% (p = 0.002)

INTEACT-2 vs. ATACH-2

Target <140 mmHg vs. <180 mmHg

"pre-specified treatment protocol based on local availability of agents"

- 30% α-antagonist (urapidil)

-16% CCB (nicardipine)

-14% labetalol, 14% NTG

-12% NTP, 12% furosemide

-6% hydralazine

(50% CIVI use)

Achieve ~ 150mmHg vs. 164 mmHg

Some improved outcomes?

Hematoma expansion numerically better

No harm

CIVI nicardipine 5mg/h

-↑ to max 15mg/h

-add IV labetalol (or diltiazem/urapidil if labetalol not available)

Achieve ~ 129 mmHg vs. 141 mmHg

No improved outcomes

Hematoma expansion numerically better

Renal adverse events

Not just the number

- BP variability
  - Standard deviation or coefficient of variation of mean blood pressure
    - Measured from 1-24h; excluding 1st hour
  - "how smooth or consistent is the control over the time period"

- Magnitude
  - The difference between SBP at randomisation and the lowest attained systolic blood pressure within 1h

Lancet Neurol 2014;13:364-73.

Lancet Neurol 2019;857-64.

Not just the number

- Post-hoc analysis of INTERACT-2 data
  - Variability = Mean SD of SBP in 1st 24h = 14.3 mmHg
  - ↑ SD of SBP significantly associated with
    - greater intensity of BP lowering regardless of target group
  - Linear association between ↑ SD and poor outcome at 90d
- Authors conclusion:
  - rapid reduction then smooth/sustained BP management may be key to improved outcomes

Lancet Neurol 2014;13:364-73.

Not just the number

- Pooled analysis of individual patient-level data from INTERACT-2 and ATACH-2 (N=3829)

- Average patient
  - 63yo; 63% male; 65% Asian ethnicity
  - NIHSS 11, randomized 3.6h from time of onset
  - 40% treated with multiple agents to reduce SBP

- Results
  - Mean magnitude drop in 1h = 29 mmHg
  - Mean SBP achieved in 1st 24h = 147 mmHg
  - Mean variability in 1st 24h = 14 mmHg

Lancet Neurol 2019;857-64.

Pooled analysis: Significant results

- Achieved SBP
  - Inverse linear association with favourable shift in functional status
  - Association with hematoma expansion and death
- Variability
  - Association with good outcome and functional independence
  - Association with hematoma expansion and death
  - Association with episodes of hypotension
- No linear association between magnitude drop and outcomes
  - Large reductions > 60 mmHg associated with lower odds of good outcome

Lancet Neurol 2019;857-64.

So how do we apply this?

- Questions not yet successfully answered
  - What is the most appropriate SBP target?
  - Is an SBP number the right goal?
    - A proportional decrease to minimize magnitude change?
    - A narrow range to minimize variability?
  - Does IV bolus vs. CIVI impact outcome given presumed correlation with variability?

Guidelines

	Recommendation	Level of Evidence
AHA/ASA ICH 2010	If SBP > 200 mmHg – aggressive reduction with CIVI If SBP > 180 mmHg – modest reduction to 160 mmHg with prn or CIVI Acute lowering to 140 mmHg is probably safe	Class IIb, level C Class IIb, level C Class IIa, level B ← INTERACT-2
AHA/ASA ICH 2015	"acute lowering of SBP to 140 mmHg is safe" "can be effective for improving functional outcome" "aggressive reduction" if SBP > 220 with CIVI	Class I, level A Class IIa, level B Class IIb, level C ← ATACH-2
ACC/AHA HTN 2017	SBP lowering to <140 mmHg within 6 hours is not of benefit to reduce death or severe disability and can be potentially harmful	Class IIa, level C (expert opinion) Class III, level A
Hypertension Canada 2018	SBP lowering to <140 mmHg should be avoided due to an absence of benefit (relative to target of <180 mmHg) and some suggestion of harm	Grade A
Canadian Stroke Best Practices 2020	To be published next week ☹	

Clinical Practice at VGH: A pharmacists perspective

- Multiple SBP targets ordered
  - Prescribed by intensivist or neurosurgery or ERP
    - Differing based on patient specific factors, prescriber preference, previous patient experiences
- Primary agents
  - IV prn (labetalol, hydralazine, enalaprilat)
  - Range of doses/frequencies
  - Unclear how often we are achieving our prescribed target
    - Perception of very frequent prn use

Research Question

In patients admitted to our ICU with spontaneous intracerebral hemorrhage, what is the target blood pressure prescribed, how quick and effective are we in achieving that target, and what are the clinical outcomes of these patients.

Research Team

- Primary researcher
  - David Tom, PharmD, Pharmacy Resident
- Primary preceptor
  - Erica Otto, BScPharm, ACPR, PharmD
- Co-preceptors:
  - Curtis Harder, BScPharm, ACPR, PharmD
  - Laura Yoo, BScPharm, ACPR
- ICU stakeholders
  - Lorne Porayko, MD
  - Grant McIntyre, MD

Targeted Approach to Pressure in IntraCerebral Hemorrhage (TAP-ICH)

Thoughts??

- Order set?
  - For hypertension?
  - Specifically for ICH
- Standardized approach/protocol
    - 2-3 doses IV bolus then CIVI for 1st 24h?
- Additional agents
  - Nicardipine special access?
  - More labetalol infusions

IV agent comparisons

Agent	Recommended Dosing	Peak effect	Duration	Cost $)
Labetalol	10-20mg IV push q15 min Max 10mg/min Max 80mg/dose 0.5-2 mg/min CIVI Max 10mg/min	5-15 min	16-18h t1/2 ~5.5h	6.24/100mg vial
Hydralazine	5-10mg IV over 15-30 min q20-30 min Max 40mg/dose	10-80 min	1-4 h (up to 12h) t1/2 3-7h	8.99/20mg vial
Enalaprilat	1.25mg-5mg q6h Incremental dosing q15-60min; Max 5mg in 6 hours	1- 4 hours	~6 hours t1/2~35h	24.00/2.5mg vial
Nicardipine	5mg/h CIVI ↑ By 2.5mg/h q5-15min Max 15mg/h ↓ To 3mg/h once at goal	50% max effect at 45 min CIVI	Upon d/c CIVI, 50% ↓ effect seen in 30 min Gradual over 50h	40.00/10mg vial

Nicardipine vs. labetalol

- Retrospective chart review of ICH and SAH patients
  - N=81
    - n=10 labetalol
    - n=57 nicardipine
    - n=14 combo
  - 1° ourcome: % time spent at goal
    - No difference 88 vs. 93 vs. 66% respectively
  - Mean time to goal SBP (n=24 with BP readings in 1st h)
    - 53 min labetalol vs. 32 min in nicardipine (p=0.03)
  - Comparable BP variability, bradycardia, hypotension
  - More tachycardia in combination group

Neurocrit Care 2013;18:13-19.