Who Guides the Guidelines? Improving blood pressure control in intracerebral hemorrhage

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Learning Objectives
1. Recognize different risk factors for intracerebral hemorrhage
2. Review guideline recommendations for blood pressure control in intracerebral hemorrhage
3. Summarize recent literature regarding blood pressure targets and measurements
4. Identify optimal blood pressure reduction strategies
A. Incidence\textsuperscript{1}
   1. Worldwide incidence $\rightarrow$ 10-20 cases per 100,000
   2. United States $\rightarrow$ 37,000-52,400/year
   3. Three to four times more common in men than in women
   4. Overall mortality rate $\rightarrow$ 50%
   5. Only 20% of patients regain functional independence at 6 months

B. Risk Factors\textsuperscript{1-4}
   1. Hypertension
      a. Major cause in up to 60% of all ICH cases
      b. Patients with hypertension have triple the risk of ICH in their lifetime
   2. Anticoagulation
      a. Increases the risk of ICH by 7-10x
      b. Mortality rate associated with anticoagulated ICH $\rightarrow$ 60%
   3. Age greater than 55 doubles the risk of ICH
   4. Smoking status
      a. Risk ratio of 1.31 (95% CI 1.09 – 1.58) for current smokers vs non-smokers
      b. Risk ratio 1.06 (95% CI 0.89 – 1.26) for past smokers vs never smokers
   5. Race
      a. Black patients at 1.6x risk of ICH compared to white patients
      b. Black patients experience ICH at significantly younger age than whites (62 vs 72 years)
   6. Alcohol
      a. Moderate intake of $\leq$ 4 drinks/day 2x risk of ICH
      b. High intake of $>$ 4 drinks/day 4x risk of ICH

C. Pathogenesis\textsuperscript{1,2,8,10}
   1. Initial hemorrhage
      a. Degeneration of smooth muscle in vessel wall
      b. Up to 40% of cases include intraventricular hemorrhage (IVH), which is associated with worsened prognosis
   2. Hematoma expansion
      a. About 38% of patients will display increase in hematoma size $>33\%$ of baseline within 3h of onset
      b. Local tissue distortion, shear forces, disruption of normal anatomy $\rightarrow$ ongoing bleeding
      c. Most common within 4-6 hours of hemorrhage onset
      d. Increased hematoma burden increases ICP and tissue injury
      e. Predictors of hematoma expansion
         i. Alcohol consumption
            (i) No alcohol – 8.6%
            (ii) Mild alcohol intake (1-50g/d) - 15.3%
            (iii) Heavy alcohol intake (>50g/d) – 25%
         ii. Consciousness at admission
            (i) No disturbance in consciousness – 8%
            (ii) Disturbance in consciousness – 20%
iii. Hematoma shape
   (i) Round shape hematoma – 10.4%
   (ii) Irregular shaped hematoma – 23%

iv. Hematoma volume
   (i) Small (<10 cm³) – 6.5%
   (ii) Medium (>10 to 20 cm³) – 16.7%
   (iii) Large (>20 to 40 cm³) – 21.4%
   (iv) Huge (>40 cm³) – 29.1%

f. Implications
   i. Hematoma expansion of >33% increases risk of neurologic deterioration and death by 4.5x
   ii. Blood pressure directly affects hematoma expansion
       (i) Target SBP of ≥160 mmHg significantly associated with hematoma expansion compared to <160 mmHg target (p=0.025)
       (ii) Rates of hematoma expansion based SBP value after admission: <150 mmHg (8.4%), 150 – 175 mmHg (13.6%), >175 – 200 mmHg (14.3%), >200 mmHg (21.5%)

3. Peri-hematoma edema
   a. Primary cause of neurologic deterioration
   b. Hematoma precipitates edema and neuronal damage in surrounding tissue
   c. Edema is caused by release of serum proteins from clot
   d. Cytotoxic edema also follows breakdown of blood-brain barrier
   e. Edema usually lasts 5 days but may persist for longer

D. Predictors of poor outcome1,2,5
   1. Large hematoma volume (>30 mL)
      a. Highly dependent on area of hemorrhage
      b. >5 ml hemorrhage in certain areas can be fatal
   2. Hematoma expansion
      a. Up to 20% of patients will have hematoma expansion of 12.5 mL or more
      b. Most common within 6 hours of onset
      c. Extremely rare after 24 hours
   3. Intraventricular hemorrhage
      a. Associated with ≈ 40% of ICH cases
      b. Can lead to obstructive hydrocephalus
         i. Accumulation of cerebrospinal fluid in brain
         ii. Shunt or endoscopy needed to treat
   4. Elevated blood pressure on presentation (MAP >130 mmHg)
   5. Older age
E. Types\textsuperscript{1-2,5-6}

1. Primary intracerebral hemorrhage
   a. Spontaneous rupture of small vessels
   b. Accounts for 78-88% of cases

2. Secondary intracerebral hemorrhage
   a. Aneurysms
      i. Localized, blood filled bulge in blood vessel
      ii. Overall prevalence of 1-5%
      iii. 50-80% of aneurysms will not rupture in a person’s lifetime
      iv. Rupture most commonly leads to subarachnoid hemorrhage (SAH)
   b. Arteriovenous malformations (AVM)
      i. Tangle of arteries and veins linked by fistulas
      ii. Overall prevalence of 0.1% in US population
      iii. Account for approximately 2% of all ICH
      iv. Frequency of hemorrhage 30-82%, with associated mortality of 10-15%

Figure 1. Common sites of intracerebral hemorrhage in order of frequency

A. Basal ganglia (40-50%) B. Thalamus (20-50%) C. Pons (5-12%) D. Cerebellum (5-10%) E. Superior cerebellar arteries (1-5%)
F. Diagnosis\textsuperscript{1-2,11}
   1. Presentation
      a. Progressive onset of focal neurological deficits (abrupt change in consciousness, weakness, aphasia) over minutes to hours
      b. Headache and vomiting observed more in ICH compared with acute ischemic stroke (AIS)
   2. Severity Scoring
      a. Glasgow coma scale
         ii. Neurological scale used to assess level of consciousness
         iii. Grades patient on eye, verbal, and motor domains
      b. ICH Score
         ii. Predicts 30 day mortality
         iii. Grades patient on 5 independent predictors of mortality
   3. Imaging
      a. Computerized tomography (CT) scan to locate and size hematoma
         ii. Preferred due to speed, accuracy, and availability
         iii. Very sensitive for identifying acute hemorrhage
         iv. Acute hemorrhage appears as hyperdense (bright white)
         v. Hemorrhage will appear isodense after 1 to 2 weeks, and hypodense by 2 to 3 weeks
      b. Angiography if hemorrhage without clear cause
         ii. Helps exclude secondary causes → aneurysms, tumors, AVMs or fistulas
         iii. Contrast enhanced CT may help identify patients at risk for hematoma expansion
         iv. Extravasation of contrast into hematoma is known as a “spot sign” → independent predictor of hematoma expansion

A. Surgical\textsuperscript{1-2,12}
   1. Hematoma evacuation
      a. Patients with cerebellar hemorrhage who are deteriorating neurologically or have brainstem compression or hydrocephalus should receive surgical removal of hemorrhage
      b. Stereotactic surgery for deeper hematoma locations
         i. Image guided, minimally invasive technique
         ii. Utilize thrombolytic agents and water jets to facilitate evacuation
         iii. Potential morbidity benefit of minimally invasive techniques
   2. STICH II trial
      a. Analyzed effect of early surgical intervention vs conservative treatment
      b. Unable to detect a statistically significant difference in death or disability between groups; absolute difference 3.7% (95% CI -4.3 – 11.6%)
      c. Aggressive early surgery does not clearly benefit patients as opposed to waiting until deterioration
   3. Aneurysm\textsuperscript{6}
      a. Craniotomy with clip ligation
         i. Permanent clips placed across neck of aneurysm
         ii. Clipping an un-ruptured aneurysm → 1-3% risk associated mortality
b. Endovascular coiling
   i. Microcatheter advanced into aneurysm
   ii. Various sized coils deployed to decrease blood flow to aneurysm
   iii. Risk of rupturing aneurysm = 2% → associated mortality 30-40%

![Coil in place]

Figure 2. Coils placed in aneurysm to prevent blood flow

4. AVMs
   a. Feeding arteries are ligated to prevent blood flow to AVM
   b. Endovascular occlusion for surgically inaccessible or deep arteries
   c. Radiotherapy focused on fistulas

B. Medical

1. Airway
   a. Neurological decline may lead to loss of ability to maintain open airway
   b. Failure to properly ventilate → hypercapnia which increases intracranial pressure (ICP)
   c. Intubation indicated if patient cannot protect airway or oxygenate properly

2. ICP management
   a. Target cerebral perfusion pressure of ≥60 mmHg
   b. Ventricular drainage indicated for hydrocephalus
   c. Head of bed elevation to 30 degrees
   d. Hypertonic fluids as necessary

3. Hemostatic therapy → reverse anticoagulation if on anticoagulant medications

4. Glucose management
   a. High blood glucose is an independent predictor of mortality
   b. Target glucose level is unclear, but hypo/hyperglycemia should be avoided

5. Anticonvulsant therapy
   a. 30 day risk of clinically relevant seizures after ICH ≈ 8%
   b. Prophylactic antiepileptic drugs have not been shown to provide benefit and are not recommended
A. Background\textsuperscript{1,2,5,9}
   1. Up to 75% of patients with ICH will present with SBP $\geq 140$ mmHg
   2. Potential Causes
      a. History of uncontrolled hypertension
      b. Neuroendocrine activation – renin-angiotensin-aldosterone cascade
      c. Compensatory mechanism to maintain cerebral perfusion
      d. Damage to central autonomic centers
   3. Blood pressure as a prognostic indicator
      a. Independent predictor of early mortality and poor outcome
      b. Mean arterial pressure (MAP) on admission $\geq 145$ mmHg associated with significantly higher 30 day mortality rates (47-67\%) vs lower MAP values (21-40\%)
      c. Elevated SBP $>180$ mmHg at admission $\rightarrow$ 3-4x increased risk of death within 7 days
      d. SBP on admission associated with U-shaped mortality curve (Figure 4)
         i. Patients with admit SBP 121-140 mmHg have lowest mortality rate (14.7\%)
         ii. SBP $<101$ mmHg and SBP $>220$ mmHg associated with statistically significant higher rate of mortality (40\%, 46.7\% respectively)
      e. Low SBP after admission also associated with U-shaped curve for risk of early neurological deterioration (END) (Figure 5)

Figure 3. Admission SBP and associated mortality
Adapted from Vemmos et al.

Figure 4. OR of END according to minimum SBP after admission
Adapted from Ohwaki et al.
A. 2010 American Heart Association Guidelines\textsuperscript{14}
   1. Suggest BP target of 160/90 mmHg (IIb)
   2. “Intensive BP lowering is clinically feasible and potentially safe, the BP pressure target, duration of therapy, and whether such treatment improves clinical outcomes remain unclear”
   3. Evidence\textsuperscript{15-16}
      a. Zhang et al. analyzed 1760 hemorrhagic stroke patients across six hospitals in China
         i. Odds ratio for combined death or disability based on admission SBP:
            (i) SBP 160-179 mmHg 1.50 (95% CI 1.06 – 2.13)
            (ii) SBP of 180-199 mmHg 1.94 (95% CI 1.36 – 2.77)
            (iii) SBP ≥200 mmHg 2.03 (95% CI 1.45 – 2.85)
      b. INTERACT analyzed 404 patients presenting with intracerebral hemorrhage across Australia, China, and South Korea
         i. Intensive blood pressure lowering group of 140 mmHg vs conservative group of 180 mmHg
         ii. Trend toward lower hematoma growth in intensive group (15% vs 23%; risk reduction 36%, 95% CI 0 – 59%)
         iii. No difference in death or disability between groups
         iv. No difference in safety outcomes or neurological deterioration between groups

B. 2015 American Heart Association Guidelines\textsuperscript{13}
   1. 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 (IA)
   2. For patients with SBP >220 mmHg “consider aggressive reduction of BP” (IIb)
   3. Driven primarily by data from INTERACT\textsuperscript{2}\textsuperscript{15}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Major intracerebral hemorrhage publications}
\end{figure}

**Objective**
Determine the effectiveness of early intensive lowering of blood pressure in patients with intracerebral hemorrhage

**Study Design**
International, multicenter, prospective, randomized, open-treatment, blinded endpoint trial from October 2008-August 2012

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated to a goal blood pressure of 140 mmHg within 1 hour after randomization</td>
<td>Treated if blood pressure was &gt;180 mmHg with no lower level stipulated</td>
</tr>
<tr>
<td>Maintained for 7 days</td>
<td></td>
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</tbody>
</table>

**Primary outcome:**
- Proportion of patient with a poor outcome (defined as death or major disability (3-5 of Modified Rankin Scale))

**Secondary outcomes:**
- All-cause mortality
- Health related quality of life (EQ-5D)
- Early neurological deterioration
- Severe hypotension
- Hematoma volume change from baseline to 24 hours

**Patients**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;18 years of age</td>
<td>Structural cause for ICH</td>
</tr>
<tr>
<td>Acute stroke due to ICH</td>
<td>GCS 3-5</td>
</tr>
<tr>
<td>Two systolic BP measurements of ≥150 mmHg and ≤220 mmHg</td>
<td>Massive hematoma with poor prognosis</td>
</tr>
</tbody>
</table>

**Statistics**
2800 patients needed to have 90% power to detect a 14% relative reduction in primary outcome Alpha of 0.05 with two sided significance test Chi-square test of proportions for primary outcome Sensitivity analyses performed for baseline variables

**Results**
- 2839 patients at 144 hospitals in 21 countries included for analysis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Intensive group (1399)</th>
<th>Guidelines group (1430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 ± 13.1</td>
<td>64.1 ± 12.6</td>
<td></td>
</tr>
</tbody>
</table>

| Recruited from China | 67.7% | 68.0% |
| SBP (mmHg) | 179 ± 17 | 179 ± 17 |
| GCS | 14 | 14 |
| Alpha-adrenergic antagonist | 32.5% | 13.4% |
| Calcium-channel blocker | 16.2% | 8.5% |
| Combined alpha and beta-blocker | 14.4% | 5.8% |
| Diuretic | 12.4% | 6.6% |
| Nitroprusside | 12.1% | 2.0% |

- Primary outcome: 52% vs 55.6%, OR 0.87 (95% CI 0.75-1.01, p=0.06)
- Health utility score (EQ-5D): 0.60±0.39 vs 0.55±0.40 (p=0.002)
- Ordinal analysis of modified Rankin scale
  - 0.87, 95% CI 0.77-1.00 (p=0.04)
  - 13% reduction in odds of disability
- No significant difference in early neurological deterioration
- No significant difference in safety outcomes, including severe hypotension
- No significant difference in hematoma growth

**Authors’ Conclusions**
Early intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome, but an ordinal analysis on the modified Rankin scale did suggest improved functional outcomes

**Critique**
- Only 33% of patients in intensive group achieved BP target at 1 hour
- Only 53% of patients in intensive group achieved BP target at 6 hours
- Urapidil as primary therapy in 32.5% of patients in intensive group
- Labetalol or nicardipine used in 30.6% of patients in intensive
- Average time to treatment in intensive group was 4 hours; may obfuscate benefit
- Largest study to date analyzing intensive blood pressure lowering
B. Definitions
   1. No standardized method to report BPV
   2. Standard deviation (SD)
      a. SD of SBP most commonly used parameter to measure variability
      b. SD of DBP also reported
   3. Coefficient of variation
      a. SD divided by the mean
      b. Not often reported

C. Clinical Significance
   1. Stroke patients have decreased baroreceptor sensitivity
   2. Decreased baroreceptor sensitivity leads to an inability to regulate blood pressure
   3. Large fluctuations in blood pressure over the first 24 hours and up to 7 days after ICH have been shown to be independent predictors of poor outcomes
   4. Smooth reduction of blood pressure and maintaining a steady blood pressure level may lead to better outcomes

D. Evidence
   1. 2014 post-hoc analysis of SAMURAI-ICH
      a. BP measurements through first 24 hours of presentation
      b. SD of SBP larger in patients with neurological deterioration 19.5 vs 13.7 mmHg (p=0.001)
      c. SD of SBP odds ratio of neurological deterioration 2.75 (95% CI, 1.45-6.12)
   2. 2014 post-hoc analysis of INTERACT2
      a. BP measurements through hyperacute (24 hours) and acute (2-7 days)
      b. SD of SBP in hyperacute phase guideline group 14.9 vs 13.7 mmHg intensive group (p=0.0002)
      c. SD of SBP in acute phase guideline group 13.7 vs 12.4 mmHg intensive group (p<0.0001)
      d. Hyperacute phase: Increase of SBP variability by one SD increases risk of disability or death at 90 days by 18%
      e. Acute phase: Increase of SBP variability by one SD increases risk of disability or death at 90 days by 21%

Figure 6. BPV difference between guideline and treatment groups (SD) Adapted from Manning et al.
A. Nicardipine\textsuperscript{21-22}

1. Second generation dihydropyridine calcium channel blocker
   a. Reversible inhibition of calcium channel leads to peripheral vasodilation
   b. Potent coronary vasodilator

2. High selectivity for cerebral, renal, and coronary vessels
   a. Direct vasodilatory action in cerebral vasculature
   b. Increase in renal blood flow and glomerular filtration rate

B. Labetalol\textsuperscript{23-25}

1. Non-selective beta blocker with alpha:beta blocking ratio of 1:7
   a. Beta-blockade prevents conversion of adenosine triphosphate to cyclic adenosine monophosphate
   b. Cytosolic calcium reduced – less myocardial contraction
   c. Alpha blockade reduces systemic vascular resistance – biggest contributor to antihypertensive effect

Table 1. Nicardipine and labetalol comparison

<table>
<thead>
<tr>
<th>PK/PD/Dosing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicardipine</strong></td>
<td>• Half-life: 30 minutes</td>
<td>• Time delay in setting up infusion</td>
</tr>
<tr>
<td></td>
<td>• 2-10 minute onset</td>
<td>• Increase in heart rate</td>
</tr>
<tr>
<td></td>
<td>• 5mg/hr infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Titrate by 2.5mg/hr every 5 minutes to 15mg/hr max</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Short half-life</td>
<td></td>
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<tr>
<td></td>
<td>• Fast onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Easily titratable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Selective for cerebral and coronary vasculature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Immunomodulatory (in vitro)</td>
<td></td>
</tr>
<tr>
<td><strong>Labetalol</strong></td>
<td>• Half-life: 5.5 hours</td>
<td>• Long half life</td>
</tr>
<tr>
<td></td>
<td>• 5-10 minute onset</td>
<td>• Unpredictable dose response</td>
</tr>
<tr>
<td></td>
<td>• 20 mg initial bolus</td>
<td>• Higher rates of hypotension</td>
</tr>
<tr>
<td></td>
<td>• Repeat bolus at 10-15 minute intervals</td>
<td>• Higher rates of bradycardia</td>
</tr>
<tr>
<td></td>
<td>• 1-2mg/min infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Max cumulative dose 300mg/24hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Easy dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Decrease in heart rate</td>
<td></td>
</tr>
</tbody>
</table>
C. Background Evidence\textsuperscript{26-28}

1. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department
   a. Design
      i. Multicenter, randomized trial
      ii. Eligible patients had two SBP measurements ≥180 mmHg
      iii. Primary outcome: treatment success as defined by physician determined target BP range
   b. Results
      i. 110 nicardipine patients vs 116 labetalol patients
      ii. Average baseline SBP = 212 mmHg
      iii. More nicardipine patients achieved goal BP within 30 minutes than labetalol patients (91.7% vs 82.5%, 95% CI -18.0 to -0.6)
      iv. Nicardipine patients were over 2.5x more likely to reach goal BP within 30 minutes compared to labetalol based on multivariable regression model

2. Labetalol vs nicardipine following acute stroke
   a. Design
      i. Single center retrospective review
      ii. Primary outcome: degree of MAP reduction and blood pressure variability
   b. Results
      i. 26 nicardipine patients (58% ICH) vs 64 labetalol patients (53% ICH)
      ii. No difference in degree of MAP reduction between agents
      iii. Nicardipine exhibited significantly lower amount of BP variability (8.19 mmHg vs 10.78 mmHg \( p=0.003 \))
      iv. Labetalol required significantly more dose adjustments (4 vs 2 \( p<0.001 \))
      v. Labetalol required significantly more rescue therapy (33% vs 8% \( p=0.013 \))

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Comparison of MAP and BP variability between labetalol and nicardipine patients}
\end{figure}

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the short-term clinical outcomes and cost of parenteral labetalol and nicardipine in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Retrospective analysis in two intensive care units at university affiliated hospitals from January 2008 to December 2010</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td>• Aged 19 years or older</td>
<td>• Received another antihypertensive agent before initiation of study drugs</td>
</tr>
<tr>
<td>• SBP &gt;160 mmHg or DBP &gt;90 mmHg</td>
<td>• Received study drugs for minimum of 2 hours</td>
</tr>
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<table>
<thead>
<tr>
<th>Analysis</th>
<th>Efficacy evaluation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Physician specified BP target used as efficacy endpoint</td>
<td>• No significant difference in magnitude of change in SBP</td>
</tr>
<tr>
<td>• Attainment of BP reading within ±10 mmHg of target considered success</td>
<td>• Proportion of patients achieving treatment success higher in nicardipine group (83% vs 67% p=0.04)</td>
</tr>
<tr>
<td>• If no physician specified target, then BP of 140/90 but greater than 90/60 considered treatment success</td>
<td>• Proportion of patients requiring conversion to alternative antihypertensive higher in labetalol group (31% vs 17% p=0.01)</td>
</tr>
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<table>
<thead>
<tr>
<th>Statistics</th>
<th>Mann-Whitney test used for continuous data</th>
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<tbody>
<tr>
<td>Fisher exact test used for nominal data</td>
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</tr>
<tr>
<td>Bootstrap method used to estimate 95% confidence interval on non-normally distributed data</td>
<td></td>
</tr>
<tr>
<td>P-value of 0.05 considered statistically significant</td>
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<table>
<thead>
<tr>
<th>Results</th>
<th>Baseline demographics:</th>
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<tbody>
<tr>
<td>Labetalol (n=189)</td>
<td>Nicardipine (n=193)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.2 ± 11.1</td>
</tr>
<tr>
<td>Stroke (undefined)</td>
<td>9%</td>
</tr>
<tr>
<td>Baseline SBP (mmHg)</td>
<td>172.4 ± 28.3</td>
</tr>
<tr>
<td>Average hourly dose (mg/h)</td>
<td>37.3 ± 9.4</td>
</tr>
<tr>
<td>Duration of therapy (h)</td>
<td>8.2 ± 6.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy evaluation:</th>
</tr>
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<tr>
<td>• No significant difference in magnitude of change in SBP</td>
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<thead>
<tr>
<th>Hypotension</th>
<th>19%</th>
<th>10%</th>
<th>p=0.04</th>
</tr>
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<tbody>
<tr>
<td>Bradycardia/AV block</td>
<td>12%</td>
<td>3%</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>61%</td>
<td>48%</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypotension</th>
<th>Labetalol bolus (n=67)</th>
<th>Labetalol infusion (n=122)</th>
<th>p=0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average hourly dose (mg/h)</td>
<td>80.1</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy (h)</td>
<td>2.5 ± 1.8</td>
<td>11.3 ± 8.6</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Proportion of patients with treatment success</td>
<td>55%</td>
<td>73%</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Hypotension</td>
<td>30%</td>
<td>13%</td>
<td>p=0.01</td>
</tr>
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<td>Bradycardia/AV block</td>
<td>18%</td>
<td>8%</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Total events</td>
<td>79%</td>
<td>51%</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

| Authors’ Conclusions | Nicardipine is a more effective antihypertensive than labetalol in critically ill patients in the ICU setting and has a more favorable adverse event profile. |

| Critique | |
|-----------||
| • Retrospective review without randomization or blinding |
| • BP goals not clearly defined and subject to physician discretion |
| • Labetalol infusion not directly compared to nicardipine infusion |

### Objective
Evaluate the efficacy and safety of nicardipine and labetalol for blood pressure management in acutely hypertensive stroke patients

### Study Design
Prospective, single-center, pseudo-randomized trial

<table>
<thead>
<tr>
<th>Nicardipine Group:</th>
<th>Labetalol Group:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5mg/hour IV infusion</td>
<td>20 mg IV bolus</td>
</tr>
<tr>
<td>Titrated by 2.5mg/hr every 15 minutes</td>
<td>Repeat dosing every 15 minutes as needed</td>
</tr>
<tr>
<td>Max rate of 15mg/hour</td>
<td>Max cumulative dose of 300mg/day</td>
</tr>
</tbody>
</table>

- BP goals (mmHg): ICH (<180), AIS (<185 or <220 depending on thrombolytic use), SAH (<160)
- Vital signs taken every 15 minutes until goal BP achieved
- Primary outcome: proportion of patients with goal BP achieved
- Secondary outcomes: Time spent within goal BP, BPV, adverse effects

### Patients

**Inclusion:**
- >18 years of age
- Primary intracranial hemorrhage (ICH)
- Subarachnoid hemorrhage (SAH)
- Acute ischemic stroke (AIS)

**Exclusion:**
- Acute brain injury was traumatic
- History of intracranial neoplasm
- Any IV antihypertensive within preceding 24h
- Brainstem herniation
- Imminent death

### Statistics
- 25 patients in each arm needed to find difference in goal BP at 60 minutes
- 2-sided alpha of 0.05 and beta of 0.8
- Continuous variables: student’s t test or Mann-Whitney U test
- Dichotomous variables: Pearson’s Chi square or Fisher’s exact test

### Results

<table>
<thead>
<tr>
<th></th>
<th>Labetalol (n=28)</th>
<th>Nicardipine (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 (48-62)</td>
<td>58 (49-67)</td>
</tr>
<tr>
<td>ICH (n, %)</td>
<td>13 (46)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>AIS</td>
<td>10 (36)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>SAH</td>
<td>5 (18)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Admit SBP (mmHg)</td>
<td>208 ± 26</td>
<td>215 ± 20</td>
</tr>
</tbody>
</table>

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Labetalol (n=28)</th>
<th>Nicardipine (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study SBP (mmHg)</td>
<td>182 ± 21</td>
<td>159 ± 11</td>
</tr>
<tr>
<td>SBP SD (mmHg)</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Time spent within goal BP (%)</td>
<td>36%</td>
<td>89%</td>
</tr>
<tr>
<td>Goal BP achieved (n,%)</td>
<td>17 (61%)</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Goal BP achieved within 60 minutes (n, %)</td>
<td>7 (25%)</td>
<td>23 (89%)</td>
</tr>
<tr>
<td>Rescue therapy required (n, %)</td>
<td>20 (77%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Authors’ Conclusions
Nicardipine provides a more predictable BP response with less variation compared to labetalol during the first 24h following stroke

### Critique
- Not powered to show difference in hematoma volume
- Utilized old BP goals
- Lacking report on clinical outcomes
- Small sample size and single center
A. Conclusion
   1. Blood pressure control is stroke is an extremely important facet of care
   2. BP variability may play a larger role in outcomes than previously thought
   3. The two most studied agents differ in their mechanism and kinetic profiles

B. Recommendation
   1. Nicardipine infusion for all patients (whom contraindications do not exist) presenting with ICH who have a blood pressure >140 mmHg for at least 24 hours from event
      a. Starting infusion rate for 140-149 mmHg: 3 mg/hr
      b. Starting infusion rate for >150 mmHg: 5 mg/hr
   2. Continuous blood pressure monitoring or measurements every 15 minutes for first 24 hours after event
      a. Blood pressure goal of 130-140 mmHg
      b. Emphasis on minimizing wide variations in blood pressure once goal range reached
   3. Transition to oral antihypertensive medication after 24 hours for eligible patients
   4. Labetalol infusion if nicardipine is not available or contraindicated
      a. Initial infusion rate of 0.1mg/min → max rate of 0.2mg/min
      b. Caution in exceeding 300mg total daily dose
   5. Labetalol bolus if infusion is not available

II. Future Directions
A. ATACHII
   1. Multicenter, randomized, blinded trial investigating the use of nicardipine infusion in ICH
   2. Hypothesize that SBP reduction to ≤140 mmHg reduces death or disability at 3 months by at least 10% compared to reduction to ≤180 mHg
   3. Will more accurately reflect current US practice than INTERACT2

B. Clevidipine
   1. Dihydropyridine calcium channel blocker
   2. ACCELERATE Trial
      a. Analyzed 35 patients with ICH and hypertension
      b. Median time to target SBP (≤160mmHg to ≥140mmHg) 5.5 minutes
      c. Clevidipine monotherapy achieved target in 96.9% of patients
   3. Demonstrated to be safe in ICH
   4. Further investigation warranted regarding efficacy versus nicardipine
Appendices

Appendix A. Glasgow Coma Scale (GCS)

<table>
<thead>
<tr>
<th>Glasgow Coma Scale</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Opening Response</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneous-open with blinking at baseline</td>
<td>4</td>
</tr>
<tr>
<td>To verbal stimuli, command, speech</td>
<td>3</td>
</tr>
<tr>
<td>To pain only</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td><strong>Verbal Response</strong></td>
<td></td>
</tr>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused conversation, but able to answer questions</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible speech</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td><strong>Motor Response</strong></td>
<td></td>
</tr>
<tr>
<td>Obeys commands for movement</td>
<td>6</td>
</tr>
<tr>
<td>Purposeful movement to painful stimulus</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws in response to pain</td>
<td>4</td>
</tr>
<tr>
<td>Flexion in response to pain</td>
<td>3</td>
</tr>
<tr>
<td>Extension in response to pain</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

Appendix B. ICH Score

<table>
<thead>
<tr>
<th>Component</th>
<th>ICH Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS score</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
</tr>
<tr>
<td>5-12</td>
<td>1</td>
</tr>
<tr>
<td>13-15</td>
<td>0</td>
</tr>
<tr>
<td>ICH Volume, cm$^3$</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>1</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
</tr>
<tr>
<td>IVH</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Infratentorial origin</td>
<td>Yes</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Age, years</td>
<td>≥80</td>
</tr>
<tr>
<td>&lt;80</td>
<td>0</td>
</tr>
</tbody>
</table>

Appendix C. Modified Rankin Scale

<table>
<thead>
<tr>
<th>Modified Rankin Scale for Neurologic Disability</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Symptoms</td>
<td>0</td>
</tr>
<tr>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
<td>1</td>
</tr>
<tr>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
<td>2</td>
</tr>
<tr>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
<td>3</td>
</tr>
<tr>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
<td>4</td>
</tr>
<tr>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
<td>5</td>
</tr>
<tr>
<td>Dead</td>
<td>6</td>
</tr>
</tbody>
</table>

References:


