Management strategy in hypertensive crisis: the role of nicardipine

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Hypertensive crisis

Sudden increase
SBP>180/DBP>120 mmHg

ACUTE END-ORGAN DAMAGE

Hypertensive urgency (HT URG)

Hypertensive emergency (HT EMG)
HT crisis pathophysiology

 ↑ Circulating vasoconstrictor

 Arteriolar necrosis

 Ischemia & organ damage

 ↑ Systemic vascular resistance (SVR)

 ↑ Blood pressure

 Endothelial damage
 Loss of autoregulation
ENCEPHALOPATHY
PAPILLEDEMA
AORTIC DISSECT.

STROKE
MYOCARDIAL ISCHEMIA
LEFT VENTR. FAILURE

END-ORGAN DAMAGE
Management principles

GOAL

• To break the cycle of increasing SVR & BP,
• Preserve cardiac output
• Maintain renal blood flow
• Prevent / limit target organ damage
Management principles

- Rapidity of BP lowering determine type & setting of treatment
- Type of treatment: parenteral or oral
- Setting: ICU, ward or one day care
- Depend on the presence of acute end-organ damage
BP autoregulation

- Brain, heart, kidney have BP autoregulatory mechanisms
- Maintain blood flow at near constant levels despite BP fluctuations;
- Autoregulation fails in sudden increase of BP
- Most vulnerable is brain; it is enclosed in finite space, and maximally extracts oxygen at baseline
Brain BP autoregulation

- Cerebral blood flow is closely regulated, directly related to cerebral perfusion pressure (CPP)
- CPP = mean arterial pressure (MAP) – intracranial pressure (ICP)
- MAP = DBP + 1/3 pulse pressure
- CPP ↓ below AR → brain infarction
- CPP exceeds AR → hyperperfusion → cerebral edema, elevated ICP

Implication: 25% MAP reduction
Hypertensive urgency

- Severe HT without acute end-organ damage
- Most patients have chronic HT who are suboptimally treated or noncompliant.
- Most HT URG are not in immediate danger of progressing to HT EMG.
Management in HT URG

- Modestly lower BP in period of hours to days, target $\leq 160/100$
- Rapidity based on individual risk for adverse event & probable duration of severe HT
- Avoid overtreating & inciting hypotensive complications
- Treat with oral agent
- Agents: nitrate, captopril, clonidine, labetalol

* Not available in Indonesia
Management in HT URG

• Manage in a quiet room to rest $\rightarrow$ $\downarrow$ 10 to 20 mmHg
• Can often be managed outpatient, as long as adequate monitoring is ensured
• Monitoring every 4-6 hours for BP and possible complications
• if not possible, admit to one day care ward, or observe in emergency unit
Hypertensive emergency

- BP >180/120 mmHg with signs/symptoms of target organ damage
- Symptoms of HT EMG: severe headache, blurred vision, confusion, seizure, chest pain, shortness of breath.
- Signs of HT EMG: altered consciousness, neurologic deficits, grade III or IV retinopathy, rales, S3 gallop, pulse deficits.
## Prevalence of HT Emergency Manifestations

<table>
<thead>
<tr>
<th>End Organ Damage</th>
<th>Case (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Infarction</td>
<td>24.5</td>
</tr>
<tr>
<td>Acute Pulmonary Edema</td>
<td>22.5</td>
</tr>
<tr>
<td>Hypertensive Encephalopathy</td>
<td>16.3</td>
</tr>
<tr>
<td>Acute Congestive Heart Failure</td>
<td>14.3</td>
</tr>
<tr>
<td>Acute Myocardial Infarction or Unstable Angina</td>
<td>12.0</td>
</tr>
<tr>
<td>Intracerebral or Subarachnoid Bleed</td>
<td>4.5</td>
</tr>
<tr>
<td>Aortic Dissection</td>
<td>2.0</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Clanigan JS, Vitberg D. Med Clin N Am, 2006
Hypertensive encephalopathy

- Elevated BP $\rightarrow$ cerebral edema $\rightarrow$ symptoms
- Severe headache, irritability, altered consciousness
- Usually in previously normotensive who experience rapid rise in BP
- Chronic hypertensive patients relatively resistant to encephalopathy due autoregulatory adaptation
Management of HT EMG

- Immediate but controlled reduction of MAP
- Treat with parenteral drug, in ICU
- ↓ MAP by 25% over minutes to 1 hr, then to 160/100 mm Hg within the next 2 to 6 hr.
- Further reductions to <140/90 within 24-48 hr to allow autoregulation to reset
- Exceptions: aortic dissection, LV failure and pulmonary edema, needs faster reduction
Drug therapy in HT urgency

• Choice of agent depends on clinical setting

• Ideal agent should have
  – Relatively fast duration of onset
  – Does not cause too large and too rapid reduction in BP
  – Predictable BP reduction
  – User familiarity

• Agents: ISDN, captopril, clonidine.
Isosorbide dinitrate

- Onset of action: SL tablet: ~3 minutes; Oral: ~1 hour; duration: Sublingual tablet: 1-2 hours; Oral: Up to 8 hours
- History of Ischemic heart disease or known coronary artery disease.
- ↓ cardiac oxygen demand by decreasing preload (left ventricular end-diastolic pressure); may modestly reduce afterload.
- Additionally, coronary artery dilation improves collateral flow to ischemic regions
Nifedipine

• Sublingual Nifedipine is contraindicated due to too rapid and too large reduction of BP
• The degree of blood pressure reduction cannot be controlled or predicted,
• Severe ischemic complications were reported with SL nifedipine
Captopril

- Fastest acting oral ACE inhibitor
- Onset/duration: 15-30 min/4-6 h
- Dose: 6.25-25 mg/every 6 h
- Rarely causes marked hypotension although possible in patients with volume depletion or renal artery stenosis
- Precaution/contraindicated in renal disease
- Chewed to increase bioavailability by buccal absorption
Clonidine

- Acts through central $\alpha$-agonist activity
- Onset/duration: 30-60 min/6-12h
- Dose: 0.1-0.2 mg/every 8-12h
- Adverse effect: sedation, rebound hypertension if stopped abruptly
- Should not be given to patients with altered sensorium or who is low compliant
Drug therapy in HT EMG

• Choice of agent depends on clinical setting
• Ideal agent should have
  — rapid onset and cessation of action,
  — predictable dose-response curve,
  — minimal side effect
  — user familiarity
• Agents: sodium nitroprusside*, nitroglycerin, nicardipine, diltiazem, labetalol*, enalapril*

* Not available in Indonesia
## Parenteral Drugs for HT Emergencies

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>0.25-10 ugr/kg/min</td>
<td>Immediate</td>
<td>1-2 minutes after infusion stopped</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-500 ug/min</td>
<td>1-3 minutes</td>
<td>5-10 minutes</td>
</tr>
<tr>
<td>Labetalol HCl</td>
<td>20-80 mg every 10-15 min or 0.5-2 mg/min</td>
<td>5-10 minutes</td>
<td>3-6 minutes</td>
</tr>
<tr>
<td>Fenoldopan HCl</td>
<td>0.1-0.3 ug/kg/min</td>
<td>&lt;5 minutes</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td><strong>Nicardipine HCl</strong></td>
<td>5-15 mg/h, titrasi dosis 2,5 mg/h setiap 10 menit</td>
<td>5-10 minutes</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td>Esmolol HCl</td>
<td>250-500 ug/kg/min IV bolus, then 50-100 ug/kg/min by infusion; may repeat bolus after 5 minutes or increase infusion to 300 ug/min</td>
<td>1-2 minutes</td>
<td>10-30 minutes</td>
</tr>
</tbody>
</table>

Chobanian AV et al, The JNC 7 report, JAMA 2003;389-2560-70
Nitroglycerin (NTG) iv

• Primarily a venodilator, has modest effects on afterload at high doses
• Drug of choice in setting of myocardial ischemia, acute MI and congestive heart failure
• NTG directly increases cerebral blood flow and raises intracranial pressure \( \rightarrow \) precaution in conditions with high ICP
• Dose: 5-200 \( \mu \)g/min infusion
• Onset/duration: immediate/3-5 min
Nicardine

- Dihydropyridine calcium channel blocker
- Potent arteriodilator $\rightarrow \downarrow$ afterload/SVR
- Particularly useful in neurological scenarios, as it does not raise ICP and directly reduces cerebral ischemia
- Has mild negative inotropic effect.
- Precautions in heart block, LV dysfunction, acute coronary syndrome, & renal failure
Nicardipine

- Onset/duration: 5-10 min/1-4h
- Initial dose: 5 mg/hr
- Titrated by 2.5 mg/hr every 5 min (for rapid titration) to every 15 min (for gradual titration), up to 15 mg/hr.
- After response is achieved, dose ↓ to & maintained at 3 mg/hr.
## Comparison between Calcium Antagonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>Coronary Vasodilation</th>
<th>Suppression of Cardiac Contractility</th>
<th>Suppression of SA Node</th>
<th>Suppression of AV Node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil (phenylalkylamine)</td>
<td>++++</td>
<td>++++</td>
<td>+++++</td>
<td>+++++</td>
</tr>
<tr>
<td>Diltiazem (benzothiazepin)</td>
<td>+++</td>
<td>++</td>
<td>+++++</td>
<td>+++</td>
</tr>
<tr>
<td>Nicardipine (dihydropyridine)</td>
<td>+++++</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Kerins DM. Goodman Gilman’s. 10th ed. 2001: 843-70
Pharmacodynamic effects of Nicardipine On Vascular/Hemodynamic

- Transmembrane influx of calcium ions into the cardiac and smooth muscle without altering serum concentration
- Systemic vascular resistance
- Systolic BP, diastolic BP, MAP
- Antispastic effects in radial artery in vitro

*Drugs 2006 (66) 13*
Pharmacodynamic effects of Nicardipine on Cardiac

- Heart rate, secondary to reflex sympathetic activation
- Coronary blood flow
- Low incidence of no-flow during PCI
- Cardiac output, stroke volume and LV ejection fraction
- Myocardial ischaemia during transient occlusion of the proximal left anterior descending coronary artery
- LV lactate productions in pts with angina pectoris
- No detrimental effects on cardiac conduction system.
Pharmacodynamic effects of Nicardipine On Cerebrovascular

- **Cerebral Vascular Resistance**
- Did not increase ICP compared with placebo in pts with severe head injury
- **Cerebral blood flow in ischaemic areas and the middle cerebral artery**
- **Cerebral blood flow in the internal carotid artery and local cerebral blood flow during aneurysm clipping**

*Drugs 2006 (66) 13*
### Drug of Choice of Hypertensive Emergencies Treatment based on CHEST 2007

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Preferred Antihypertensive Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pulmonary edema/systolic dysfunction</td>
<td><strong>Nicardipine, fenoldopam, or nitroprusside in combination with nitroglycerin and a loop diuretic</strong></td>
</tr>
<tr>
<td>Acute pulmonary edema/diastolic dysfunction</td>
<td>Esmolol, metoprolol, labetalol, or verapamil in combination with low-dose nitroglycerin and a loop diuretic</td>
</tr>
<tr>
<td>Acute myocardial ischemia</td>
<td>Labetalol or esmolol in combination with nitroglycerin</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td><strong>Nicardipine, labetalol, or fenoldopam</strong></td>
</tr>
<tr>
<td>Acute aortic dissection</td>
<td>Labetalol or combination of <strong>nicardipine</strong> and esmolol or combination of nitroprusside with either esmolol or IV metoprolol</td>
</tr>
<tr>
<td>Pre-eclampsia, eclampsia</td>
<td>Labetalol or <strong>nicardipine</strong></td>
</tr>
<tr>
<td>Acute renal failure/microangiopathic anemia</td>
<td><strong>Nicardipine</strong> or fenoldopam</td>
</tr>
<tr>
<td>Sympathetic crisis/cocaine overdose</td>
<td>Verapamil, diltiazem, or <strong>nicardipine</strong> in combination with a benzodiazepine</td>
</tr>
<tr>
<td>APH</td>
<td>Esmolol, <strong>nicardipine</strong>, or labetalol</td>
</tr>
<tr>
<td>Acute ischemic stroke/intracerebral bleed</td>
<td><strong>Nicardipine, labetalol, or fenoldopam</strong></td>
</tr>
</tbody>
</table>

Adapted from: CHEST 2007.
**Therapeutic Guideline (ASA 2010)**

<table>
<thead>
<tr>
<th><strong>TREATING ARTERIAL HYPERTENSION IN ACUTE ISCHEMIC STROKE: RECOMMENDATIONS, 2007, 2010</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When IV reperfusion therapy is indicated and blood pressure is &gt;185/110 mm Hg</strong></td>
</tr>
<tr>
<td><strong>2007 RECOMMENDATIONS</strong></td>
</tr>
<tr>
<td><strong>BP level</strong></td>
</tr>
<tr>
<td><strong>Recommended IV antihypertensive options</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Reperfusion is contraindicated</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Take home messages

• HT crisis consists of two subsets based of presence of end-organ damage: HT EMG & URG

• In HT URG, patients can be managed outpatient or one day care; BP can be reduced within hours to days, using oral agents.
Take home messages

• In HT EMG, patients should be admitted to ICU; MAP should be reduced by no more than 25% in minutes to 1 hour, using parenteral drugs.

• Nicardipin merupakan pilihan tepat untuk kasus hipertensi emergensi

THANK YOU...
**Diltiazem**

- Diltiazem 10mg IV given in 1-3 min, continue with infusion 50 mg/h in 20 min.
- If BP has reduced >20%, dose is given 30 mg/h until target is reached.
- Maintenance dose 5-10 mg/h for 4 h, then switch to oral agent.
- Contraindicated in conduction problem and LV dysfunction.
- Preparates: diltiazem (Herbesser) iv (10 mg & 50 mg/ampoule)
Reduction of MAP with diltiazem

- 29 Severe Hypertensive Patients
  - After 1 hr time evaluation
  - Average infusion Rate: 11 µg/kg/mnt.
  - Result:

<table>
<thead>
<tr>
<th>Pretreatment:</th>
<th>After treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP: 205.6-224</td>
<td>Avg: SBP: 154.0</td>
</tr>
<tr>
<td>DBP:115.8</td>
<td>DBP: 83.3</td>
</tr>
<tr>
<td>MABP: 145.7</td>
<td>MABP: 113.4</td>
</tr>
</tbody>
</table>

- 11 Hypertensive Crisis Patients
  - Average time evaluation 3.5 hr
  - Infusion Dossage: 5-40 µg/kg/mnt.
  - Result:

<table>
<thead>
<tr>
<th>Pretreatment:</th>
<th>After treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP: 224-DBP:136</td>
<td>Avg: SBP: 170-DBP:</td>
</tr>
<tr>
<td>MABP: 165.7</td>
<td>95</td>
</tr>
<tr>
<td>MABP: 120</td>
<td></td>
</tr>
</tbody>
</table>


Subject: 11 patients with hypertension emergency

Design: Open study

Dosage: HERBESSER; 5~40 μg/kg/min

Hypertensive Emergency

- HERBESSER injection Drip infusion:
  - 5~40 μg/kg/min

- Average BP reduced
  - 224/119 mmHg to 170/95 mmHg
  - (mean change 27.3 ±9.0 %, P<0.001)

- HR did not change significantly

Current Therapeutic Research 42:1223,1987
Effect of a diltiazem on severe systemic hypertension

Subjects: 29 severe systemic hypertension
Dosage: diltiazem initial dose less 10 μg/kg/min, average infusion rate was 11 μg/kg/min

* P≤0.05 vs pretreatment level