

# Thrombolysis

## 1. 정맥내 혈전용해술

급성기 뇌경색 환자로서 아래 기준에 해당하는 경우 정맥내 혈전용해술의 대상이 되며, 가급적 최단시간내에 정맥내 혈전용해술을 시행하는 것을 목표로 한다.

### 1.1 정맥내 혈전용해술의 적응증 (1,2)

#### Inclusion criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <4.5 hours before beginning treatment

#### Exclusion criteria

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- Intracranial neoplasm, arteriovenous malformation, or aneurysm (anytime)
- Recent intracranial or intraspinal surgery (within previous 3 months)
- Major surgery or serious trauma within previous 14 days
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute myocardial infarction (within previous 3 months)
- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) → 약물로 혈압이 범위내로 조절되면 투여가능
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to
  - Platelet count <100,000/mm<sup>3</sup>
  - Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
  - Current use of anticoagulant with INR >1.7 or PT >15 seconds
  - Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

#### Relative exclusion criteria

Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:

- Aged <18 years or ≥80 years (즉시 동맥내 혈전용해술 혹은 비급여동의하 tPA사용 고려)
- Blood glucose concentration <50 mg/dL or 400mg/dL → 혈당조절이후에도 증상 지속시 투여가능
- History of previous intracranial hemorrhage
- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Pregnancy
- Seizure at onset with postictal residual neurological impairments (Acute infarct related seizure로 여겨지며 동반된 trauma 및 출혈위험 소견이 없으면 투여고려)

## 2. 동맥내혈전용해술

정맥내혈전용해술의 시술대상에 해당하지 않거나, 정맥내혈전용해술을 시행 받은 환자 중에서 아래 동맥내 혈전용해술의 적응증에 해당할 경우 동맥내혈전용해술을 실시한다.

### 2.1 동맥내 혈전용해술의 적응증

#### Inclusion criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <8 hours for anterior circulation, <12 hours for posterior circulation before beginning treatment

#### Exclusion criteria

- No major vessel occlusion in angiographic study (CT angio 소견상 major occlusion이 불명확하더라도 임상증상적으로 major artery occlusion이 의심되면 시행한다.)
- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) → 약물로 혈압이 범위내로 조절되면 수행가능
- Active internal bleeding
- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

#### Relative exclusion criteria

Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of mechanical thrombectomy carefully if any of these relative contraindications are present:

- History of previous intracranial hemorrhage

- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Acute bleeding diathesis, including but not limited to
  - Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
  - Platelet count  $<100,000/\text{mm}^3$
  - Current use of anticoagulant with INR  $>1.7$  or PT  $>15$  seconds
  - Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration  $<50 \text{ mg/dL}$  or  $400 \text{ mg/dL}$  → 혈당조절이후에도 증상 지속시 시행가능
- Seizure at onset with postictal residual neurological impairments (Acute infarct related seizure로 여겨지며 동반된 trauma 및 출혈위험 소견이 없으면 시행고려)

## 2.2 동맥내혈전용해술 실시전 환자 준비사항

- Foley insertion. L-tube의 경우 경구약제의 투여가 필수적인 경우 이외에는 삽입하지 않는다.
- IV-line set (독립적인 2개의 16G 정맥주사 line을 확보한다).
- Drug preparation (Sedation 및 응급상황에 대비하여 아래 약제를 미리 prep하고 확인한 뒤 angio방으로 이동한다).

약제명	개별 용량	개수
Remifentanyl	1mg	1
Fentanyl	100ug	2
Naloxone	0.4mg	2
Midazolam	5mg	2
Diazepam	10mg	1
Pentothal	0.5g	1
Hydralazine	20mg	1
Labetalol	100mg	2
Atropine	0.5mg	4
Ephedrine	40mg	1
Urokinase	10만Unit	2
Aggrastat	0.25mg	1

- 모든 사전준비시간을 최소화하여 가능한 빠른 시간내에 혈전용해술이 시작될 수 있도록 한다.

## 3. 혈전용해술시 환자 management

### 3.1 혈전용해술 환자 monitoring

- 3.1.1 시술전 자동 혈압계 및 산소 포화도 측정기를 환자에게 부착하고 15분간격으로 측정 되도록 한다.
- 3.1.2 산소포화도가 94%미만으로 떨어지지 않는 한 O<sub>2</sub> supply는 시행하지 않는다. (94%미만으로 떨어질 경우에는 O<sub>2</sub>를 공급한다.)

### 3.2 혈전용해술 환자의 혈압관리

- 3.2.1 혈전용해술대상 뇌경색 환자의 혈압은 180/105 미만으로 유지하는 것을 원칙으로 한다 (치료전, 치료후 공통).
- 3.2.2 지나친 고혈압으로 혈전용해술의 금기에 해당하는 경우
  - 환자의 혈압이 185/110을 넘어 혈전용해술의 금기에 해당할 경우 아래 Table의 순서에 따라 혈압조절을 시도한다. (1) 적정 혈압으로 조정되면 혈전용해술을 실시한다.

**Table 9. Potential Approaches to Arterial Hypertension in Acute Ischemic Stroke Patients Who Are Candidates for Acute Reperfusion Therapy**

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg: Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time; or Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate
If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA
Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg: Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg: Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

BP indicates blood pressure; IV, intravenously; and rtPA, recombinant tissue-type plasminogen activator.

- 급성기 뇌졸중환자에서 고혈압조절을 위하여 사용이 가능한 약제들(3)

**Table 2**

Intravenous agents for management of hypertension in acute ischemic or intracerebral hemorrhagic stroke

Drug	Dose	Onset of Effect	Duration of Action
Labetalol	10–20 mg as IV bolus, over 1–2 minutes or 0.5–2.0-mg/min infusion. May repeat at 10 min	5 minutes	8–12 hours
Nicardipine	5–15 mg/hour as IV infusion, increasing the rate of infusion, 2.5 mg/hour every 5 minutes, to a maximum of 15 mg/hour	1–5 minutes	15–120 minutes
Hydralazine	10–20 mg as IV bolus or intramuscularly; repeat every 4–6 hours (maximum dose: 40 mg)	10–20 minutes	3–8 hours
Sodium nitroprusside	0.25–10 µg/kg/min as IV infusion; maximal dose for 10 minutes only	Seconds to 2 minutes after beginning of infusion	1–3 minutes
Esmolol	500 µg per kg as IV bolus over 1 minute, followed by a maintenance infusion of 50 µg/kg/min for 4 minutes. Maximal dose 300 µg/kg/min	2–10 minutes	10–30 minutes
Enalaprilat	1 mg as IV bolus injection followed in 30 minutes by 10 mg	15 minutes	12 to 24 hours
Nitroglycerin	5–100 mg/min as IV infusion	2–5 minutes	5–10 minutes

IV, intravenous.

Nicardipine is most often administered initially for patients with acute hemorrhagic stroke followed by intermittent IV labetalol, and when necessary, sodium nitroprusside.

### 3.3 혈전용해술환자의 혈당 관리

- 급성기 혈당이 60mg/dl 미만일 경우 즉각적인 교정이 필요하다. 25 mL of 50% dextrose을 천천히 투여한다.

### 3.4 동맥내 혈전용해술시 환자 sedation

- 뇌경색 환자가 협조되지 않아 동맥내혈전용해술 진행에 어려움이 있는 혹은 예상되는 경우 환자의 호흡 및 혈압에 주의하면서 sedation 약제들을 시도할 수 있음. 약제를 통한 sedation을 시도할 경우에는 반드시 해당 장소에서 의료진이 직접 환자상태를 관찰하며 airway 확보 및 CPR이 가능한 장소에서 실시하도록 한다. Fentanyl 및 Remifentanyl 등 opioid drug을 사용 후 respiration hold 및 호흡부전이 발생한 경우 회복을 위하여 IV로 Naloxone 0.4 mg를 투여한다.

#### <Sedation protocol>

Drug	Method	Comment
Remifentanyl	IV infusion: 0.02 ~ 0.05 µg/kg/min	100ml NS에 remifentanyl 1mg을 mix하여 infusion pump를 통해 투여. bolus는 호흡부전의 가능성이 있어 infusion방식으로 투여하며 0.02 µg/kg/min부터 시작하여 필요에 따라 증량한다. <u>반드시 호흡마비에 주의한다.</u> Ex) 60kg일 경우 Remifentanyl 1mg을 NS 100ml에 mix하여 10ugtt로 투여하면 0.028

		μg/kg/min 임.
<b>Fentanyl</b>	IV bolus: 25 μg, 필요에 따라 반복	호흡마비에 주의
<b>Midazolam</b>	IV bolus: 2.5~5 mg, 필요에 따라 반복	호흡마비에 주의

- <참고자료> sedative drug의 특성. Mechanical ventilation 환자를 기준으로 기술된 내용으로 bolus는 함부로 투여하지 말 것 (4)

**Table 2.** Pharmacokinetic Profile of Common Sedatives in the Neuroscience Intensive Care Unit

Drug	Half-Life	Starting Dose	Titration	Protein Binding	Metabolism/Active Metabolite
Fentanyl	30-60 min (single IV dose); hrs in repeated dosing	25-50 mcg IV every 5-10 min	0.5-2.5 mcg/kg/hr every 15-30 min, up to 50-100 mcg/hr	80%-86%	Hepatic
Remifentanyl	3-10 min after single dose	0.5-1 mcg/kg IV bolus	Infusion: 0.05-0.2 mcg/kg/min	70%	Plasma esterases
Morphine sulfate	1.5-4.5 hrs IV, IM, SQ	5-20 mg IM every 4 hrs 2-10 mg IV every 4 hrs	Caution: metabolites may accumulate; For post-operative pain (PCA): 0.2-3.0 mg and 5-20 min lockout intervals	20%-30%	Hepatic/ Morphine-3-glucuronide, Morphine-6-glucuronide
Diazepam	30-60 hrs	2 mg IV every 30-60 min	—	99%	Hepatic/ N-Desmethyldiazepam, N-methyloxazepam, oxazepam
Lorazepam	10-20 hrs	0.25 mg-1 mg IV every 5-30 min	Infusion: 0.01-0.1 mg/kg/hr	91%-93%	Hepatic
Midazolam	1-2.5 hrs	0.5-1 mg IV every 5-30 min	Infusion: 0.25-1 mcg/kg/min	97%	Hepatic/ 1-hydroxymethylmidazolam
Haloperidol	12-36 hrs	0.5-5 mg IV	—	92%	Hepatic
Droperidol	4-12 hrs	0.625-2.5 mg IV	—	92%	Hepatic
Olanzapine	21-54 hrs	2.5-5 mg PO daily	—	93%	Hepatic
Quetiapine	6 hrs	25-50 mg PO twice daily	—	83%	Hepatic/N-desalkyl quetiapine
Risperidone	20-30 hrs	0.5 mg PO	—	90%	Hepatic/ 9-hydroxyrisperidone
Dexmedetomidine	2 hrs	1 mcg/kg IV bolus over 10 min	Infusion 0.2-1.0 mcg/kg/hr	94%	Hepatic
Thiopental	3-18 hrs	1-2 mg/kg IV	1.5-5 mg/kg/hr	97%	Hepatic/pentobarbital
Pentobarbital	15-50 hrs	10-20 mg/kg IV	0.5-3 mg/kg/hr	35%-55%	Hepatic
Phenobarbital	36-117 hrs	10 mg/kg IV at 100 mg/min	50 mg/min until seizures are controlled	20%-60%	Hepatic
Fospropofol	1-2 hrs	6.5 mg/kg	1.6 mg/kg every 4 minutes	98%	Hepatic/propofol
Propofol	4-10 min	1.0-2.5 mg/kg IV (anesthesia induction); 5 mcg/kg/min IV (sedation)	Increase infusion 5-10 mcg/kg/min every 5-10 min to maintenance of 25-80 mcg/kg/min, up to 100-300 mcg/kg/min	>90%	Hepatic and extrahepatic

Abbreviations: IM, intramuscular; IV, intravenous; PCA, patient-controlled analgesia; SQ, subcutaneous; PO, oral.

1. Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ (Buddy), Demaerschalk BM, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2013 Mar 1;44(3):870-947.

2. 뇌졸중. 진료지침. 2011.
3. Feldstein CA. Early treatment of hypertension in acute ischemic and intracerebral hemorrhagic stroke: Progress achieved, challenges, and perspectives. J Am Soc Hypertens. 2014;8(3):192–202.
4. Makii JM, Mirski MA, Lewin JJ. Sedation and Analgesia in Critically Ill Neurologic Patients. J Pharm Pract. 2010 Oct 1;23(5):455–69.