Antihypertensive Drug Use in Patient With Intracerebral Hemorrhage Stroke

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ABSTRACT

Intracerebral hemorrhage (ICH) stroke is a type of stroke with the highest mortality rate, with only about 38% of patients who survived for the first year after stroke. Antihypertensive treatment one of the main therapy for reduce the mortality rate in ICH. Based on review from research study journals, peer review journals, guidelines or book about use of antihypertensive drugs in ICH stroke patient and/or hypertensive emergency, uses of nicardipine, labetalol, esmolol and enalapril can be as the first-line therapy to manage acute high blood pressure in intracerebral hemorrhage stroke if there is no contraindication or caution is present. Nicardipine, labetalol, esmolol and enalapril is four agent that reduce blood pressure in a titratable fashion and do not lead increases in intracranial pressure. Hydralazine, sodium nitroprusside and nitroglycerine can be used as alternative agent if nicardipine, labetalol, esmolol and enalapril can not be used in ICH stroke patient.

Keywords: Stroke, Intracerebral Hemorrhage, Antihypertensive Agent

INTRODUCTION

Intracerebral hemorrhage (ICH) stroke is a type of stroke with the highest mortality rate, with only about 38% of patients who can survived for the first year after a stroke[1]. ICH stroke is one of manifestation from neurologic end-organ damage due to uncontrolled blood pressure in hypertensive emergencies [2]. Hypertension and increased intracranial pressure is commonly found in patients with intracerebral hemorrhage stroke. Hypertension is the most common cause of intracerebral hemorrhage. High blood pressure can lead to further widening of the hematoma. The hematoma can trigger the occurrence of edema, which can interfere with and suppress the brain tissue then can cause increased

intracranial pressure and potentially fatal herniation syndrome [3,4,5].

Antihypertensive therapy have an important role in ICH stroke management. Meyer and Baurer demonstrated the improvement in mortality in patient with intracerebral hemorrhage who were treated with antihypertensive medication even if the result of this study were limited by the fact that the treated group had less severe symptomps [6]. Dandapani et al. have shown reduction in mortality and morbidity with the reduction of blood pressure within 2 – 6 hours after intracerebral hemorrhage, but this study did not consider variables like ICH volume, ventricular blood and initial GCS [7]. Morgenstern et al. developed a therapy guidelines for intracerebral hemorrhage stroke patients which is evidence based, one of the focus is the blood pressure therapy. With a focus on treatment of increased blood pressure, expected levels of mortality in patients can be declined [8].

Management of acute increased blood pressure in ICH stroke patient should be done immediately because of increased blood pressure may increase the risk of hemorrhage widening from the small arteries and arterioles rupture during the first hour after attack [3]. Selection of antihipertensive drug should be made with some consideration. The antihypertensive medication should be an agent that is quick in onset and whose effect is easily titratable [9]. Labetalol, nicardipine, esmolol, enalapril, hydralazine, nipride and nitroglycerine is the antihypertensive agent which is recommended by American Heart Association (AHA) [3,10]. A pharmacist should be aware about use of these drugs in management of ICH stroke patient.

METHODS

Methods use in this review is literature study. Research study journals, peer review journals, guidelines or book about use of antihypertensive drugs in ICH stroke patient and/or hypertensive emergency were collected and sorted by the type of investigational drugs. Each antihypertensive drugs will be reviewed based on the journals, guidelines or book that have been collected.

RESULT

Based on recommendation from AHA, there is 7 agent which is can be

used to treat acute increased of blood pressure in ICH stroke patient. Dosage of each agent can be seen at table 1.

A. Labetalol and Esmolol

Labetalol and esmolol are included in beta blockers drugs. Labetalol blocks β1, β2 and α adrenergic receptors thus will lowering blood pressure. Esmolol is a short acting drug that is selectively blocks β1 receptors with a very small effect or no effect on β2 receptors. Esmolol particularly efficacious in patients with increased arterial pressure, especially if there are plans for surgery. Esmolol showed decreased episodes of chest pain and clinical cardiac events compared with placebo. Can be stopped immediately if needed. Useful for patients who are likely to experience complications from beta-blockers, particularly those with reactive airway disease, mild – moderate left ventricular dysfunction, and/or peripheral vascular disease [11].

1. **Labetalol**

In human, the ratio of α- to β-blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous administration, respectively. Labetatol produces dose related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its α-blocking and β-blocking effects. Labetalol can reduce blood pressure in a titratable fashion [15]. Labetalol reduces systemic vascular resistance without reducing total peripheral blood flow. Labetalol has very little effect on cerebral circulation and is thus not associated with increased ICP in the normal brain [17].

Labetalol can be given as either repeated intravenous bolus (5 to 20 mg every 15 min) or as a continuous infusion (2 mg/min (maximum 300 mg/dl)) [3]. Because it is a nonselective β-blocker, labetalol is contraindicated in patients with reactive airway disease or chronic obstructive pulmonary disease. It may worsen or exacerbate heart failure and should not be used in patients with second- or third-degree atrioventricular block or bradycardia [17].

2. **Esmolol**

Esmolol have a rapid onset, a very short duration of action, and

no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Even if esmolol is an selective β1-receptor blockers, this preferential effect is not absolute and at higher doses it begin to inhibit β2 receptors located chiefly in the bronchial and vascular musculature [15]. An initial loading dose of 250 µg/kg esmolol intravenous push followed by a maintenance infusion of 25 to 300 µg/kg.min esmolol can be given to ICH stroke patient [3]. Esmolol do not lead to increase in intracranial pressure [15].

Side effect of esmolol incuding bradycardia. Effects of bradycardia is more common in elderly, who may be more sensitive to the bradycardiac effects. If bradycardia occurs, the effects of esmolol on heart rate are eliminated within 20 minutes after drug discontinuation. Esmolol reduces cardiac index and may worsen or exacerbate symptoms in patients with heart failure [17]. Because of that, esmolol is contraindicated in patient with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure [15].

B. Enalapril

Enalapril is an angiotensin-converting enzyme inhibitors. This agent inhibit angiotensin converting enzyme thus inhibiting the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictors, inhibition of angiotensin II can produce vasodilatation and reduce secretion of aldosteron. In addition, degradation of bradykinin also inhibited. Bradykinin levels in the blood will increase and contribute to the vasodilation effect of ACEI. Vasodilatation will directly lower blood pressure, whereas the reduced aldosterone will cause water and sodium excretion and potassium retention [12]. Intravenous enalapril is an excellent choice because it has no known effect on ICP or autoregulation [9].

Enalaprilat is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalaprilat intravenous results in the reduction of both supine and standing systolic and diastolic blood pressure. The onset of action usually occurs within fifteen minutes of administration with the

maximum effect occurring within one to four hours. The duration of hemodynamic effects appears to be dose-related. Enalaprilat is indicated for the treatment of hypertension when oral therapy is not practical [15]. The dose for enalaprilat 1,25 to 5 mg every six hours administered intravenous push, but because of the risk of precipitous blood pressure lowering, the enalapril first test dose should be 0,625 mg[3]. Angioedema is a serious but rare side effect of enalaprilat. Although rare, angioedema can be life threatening. Enalaprilat is contraindicated in patient with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema [15,16].

Table 1. Intravenous medication that may be considered for control of elevated blood pressure in patient with ICH[3]

Drug	Intravenous Bolus Dose	Continuous Infusion Rate
Labetalol	5 to 20 mg every 15 min	2 mg/min (maximum 300 mg/dl)
Nicardipine	NA	5 to 15 mg/h
Esmolol	250 µg/kg IVP loading dose	25 to 300 µg/kg.min
Enalapril	1,25 to 5 mg IVP every 6 h*	NA
Hydralazine	5 to 20 mg IVP every 30 min	1,5 to 5 µg/kg.min
Nipride	NA	0,1 to 10 µg/kg.min
Nitroglycerin	NA	20 to 400 µg/min
IVP indicates intravenous push; NA, not applicable *because of the risk of precipitous blood pressure lowering, the enalapril first test dose should be 0,625 mg		

C. Nicardipine

Nicardipine is a calcium channel blockers group which is inhibit calcium influx in muscle cells of blood vessels and myocardium [12]. Nicardipine may have unique benefits in cerebrovascular disease based on its pharmacologic profile. It crosses the blood-brain barrier and acts to vasorelax cerebrovascular smooth muscle. Although nicardipine is a cerebral vasodilator, it dilates small-resistance arterioles, so there are no significant changes in intracranial volume or intracranial pressure (ICP) [17].

Study from Deryke et all. (2008) about the comparison between nicardipine and labetalol for the management of hypertension following acute stroke, conclude that nicardipine provide an alternative to the use of labetalol with the same tolerance level and provide control of blood pressure is more uniform than labetalol [13]. Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) evaluate the treatment feasibility and safety of three escalating levels of antihypertensive treatment in subjects with acute hypertension associated with intracerebral hemorrhage using intravenous nicardipine where the patients will be administered anti-hypertensive treatment to reduce systolic blood pressure to 170-200 mm Hg. Following success of this, patients will be graduated to the next two levels of blood pressure reduction (140-170 mm Hg and 110-140 mm Hg). Conclusion of this trial is aggressive sistolik blood pressure (SBP) reduction to 110–140 mm Hg in the first 24 hours using intravenous nicardipine was well tolerated with a low risk of hematoma expansion, neurological deterioration and in-hospital mortality. The results favor pharmacological reduction of SBP in patients with acute ICH. Patients in this study have new neurological onset signs of a stroke within 12 hours of the time to evaluation and initiation of treatment with intravenous nicardipine, the total GCS score is greater than 8 at the time of enrollment and CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement less than 60 cc [14]. Nicardipine is given as continuous infusion with infusion rate 5 to 15 mg/h [3]. Nicardipine is contraindicated in patients with advanced aortic stenosis because part of the therapeutic effect of nicardipine is secondary to reduce afterload. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance [15].

D. Hydralazine, Nipride (nitroprusside Na) dan Nitroglycerine

Hydralazine, nitroprusside and nitroglycerine is a vasodilator group. All vasodilator group useful for hypertension management through relaxation of smooth muscles of arterioles, thereby lowering systemic vascular resistance. Hidralazine dilates arterioles but not in vein. Nitroprusside Na dilates arterioles and relaxes the

veins. Nitroglycerin relaxes all types of smooth muscle regardless the cause of the pre-existing muscle condition. All parts of the vascular system from large arteries through large veins will experience a relaxation response to nitroglycerin. Vena will respond at the lowest concentrations, arteries at slightly higher concentrations [12].

1. **Hydralazine**

Hydralazine is a peripheral vasodilator that causes relaxation of arteriolar smooth muscle by inhibiting calcium ion release from the sarcoplasmic reticulum. The specific mechanism of action is not known, but proposed mechanisms include blocking the release of inositol trisphosphate-induced calcium and reducing calcium turnover [17]. Hydralazine can be given as intravenous bolus with doses 5 to 20 mg every 30 minutes in intravenous push or can given as continuous infusion with infusion rate 1,5 to 5 µg/kg.min [3].

Hydralazine's half-life is 1.5 hours, its effect on BP generally persists for 2–4 hours. However, a pharmacologic effect on BP exceeds 100 hours. The prolonged effect may be due to active metabolites, tissue binding in the arteriolar wall, or a sustained effect on endothelium-derived relaxing factor. The unpredictability of response and prolonged duration of action do not make hydralazine a desirable first-line agent in most patients with hypertensive emergencies [17].

2. **Nipride (Nitroprusside Na)**

Sodium nitroprusside is a nitric oxide donor. Free-radical nitric oxide activates endovascular guanyl cyclase, causing myosin dephosphorylation and vascular smooth muscle relaxation. The drug acts on arteriolar and venous smooth muscle, reducing both preload and afterload [17]. Sodium nitroprusside is a potent vascular smooth muscle relaxant, which makes this drug very attractive in the facilitation of blood pressure reduction. Of great concern in this setting is the significant potential for this agent to not only reduce systemic blood pressure via relaxation of vascular smooth muscle, but also to cause significant increases in intracranial pressure due to dilatation of intracranial vasculature via the same mechanism [15]. Information regarding the effect of sodium nitroprusside on cerebral

blood flow is conflicting, with many studies conducted in the operating suite while patients were under the influence of various anesthetic regimens that also affect cerebral blood flow [17]. Because of this potential concern, nitroprusside is the agent that is recommended if an increase in blood pressure is higher (eg the increase in diastolic pressure over 130 mmHg) [9]. This agent can be given as continuous infussion with infussion rate 0,1 to 10 µg/kg.min [3].

3. **Nitroglycerine**

Nitroglycerin is primarily a venodilator, though dilation of arterial smooth muscle also occurs with high doses. Once nitroglycerin is converted to nitric oxide, it activates guanylate cyclase and stimulates the production of cyclic GMP (cGMP). This produces smooth muscle relaxation, mainly in the venous system, and reduces myocardial preload [17]. Nitroglycerin can be given as continuous infussion with infussion rate 20 to 400 µg/min [3]. Headache is the most common adverse effect, and methemoglobinemia is a rare complication of prolonged nitroglycerin therapy [17].

DISCUSSION AND CONCLUSION

Blood pressure management in acute intracerebral hemorrhage stroke has potential for therapeutic benefit as well as the potential to cause harm if not performed with great care. Table 2 and table 3 contain a summary of antihypertensive medications that can be used in ICH stroke patient. Nicardipine, labetalol, esmolol and enalapril is four agent that reduce blood pressure in a titratable fashion and do not lead increases in intracranial pressure. Each of these drugs works by different mechanisms and therefore may be have benefit to different patients [15,17].

Labetalol is best used when the following conditions are present : acute myocardial ischemia, aortic dissection, acute postoperative hypertension, hypertensive encephalopathy, preeclampsia, and eclampsia. Esmolol is an ideal agent for situations where the cardiac output, heart rate, and blood pressure are increased, especially when a patient is experiencing acute pulmonary edema, diastolic dysfunction, acute aortic dissection, and

acute postoperative hypertension [18]. Clinicians should be aware of the possible adverse effects associated with labetalol, especially the development of sinoatrial/atrio ventricular nodal dysfunction, such as heart block. Extra consideration must also be taken for patients with a history of restrictive airway disease, such as asthma, because of the possible development of bronchospasm. Although esmolol is cardioselective, patients with reactive airway disease should be monitored closely, even though several studies have shown esmolol to be well tolerated in patients with pulmonary disease [17,18].

In contrast to shorter-acting vasodilators for hypertensive emergency, the enalaprilat dosage is not easily adjusted. Once a bolus dose is given, a longer time is needed before the clinical effects are seen. Enalaprilat need 15 until 30 minutes to shown it effect in lowering blood pressure in hypertensive patient with an intravenous bolus administration route. If hypotension occurs, the long duration of action (12 – 24 hours) is not a favorable property [17].

Nicardipine is an antihypertensive agent which is still studied for it uses as antihypertensive agent in intracerebral hemorrhage stroke because its pharmacologic profile [17]. Result of the recent study show nicardipine use can reduce hematoma expansion, neurological deterioration and in-hospital mortality [14]. Nicardipine is an ideal agent when the following conditions are present : acute pulmonary edema, hypertensive encephalopathy, acute renal failure, sympathetic crisis, acute ischemic stroke, acute postoperative hypertension [18].

Sodium nitroprusside should uses with a great concern, because the possibility effect that can lead an increases of intracranial pressure, which would be disadvantageous in patients with hypertensive encephalopathy or cerebrovascular accident. Sodium nitroprusside may also lead to cyanide poisoning. It contains 44% cyanide by weight that is released nonenzymatically from sodium nitroprusside, with the amount released dependent on the dose. Infusions at rates of greater than 4 μg/kg per minute for 2 to 3 hours have led to cyanide levels within the toxic range. This medication is recommended for use only in patients who have normal renal

and hepatic function and when other intravenous antihypertensive medications are not available [18].

Nitroglycerine can not used simultanously because nitrat tolerence effect can occurs in patient. Tolerance may occur within 24-48 hours. Nitrate-free interval (10-12 hours/day) is recommended to avoid tolerance development [19]. Nitroglycerine uses with a great concern because it negative effect in ICP. Hydralazine has prolonged effect may be due to active metabolites, tissue binding in the arteriolar wall, or a sustained effect on endothelium-derived relaxing factor. This unpredictability of response and prolonged duration of action do not make this agent as preferable agent if other intravenous antihypertensive medications are available [17].

Table 2. Parenteral antihypertensive agent used in intracerebral hemorrhage stroke which can be used as first-line therapy

Agent	Mechanism of action	Onset and duration	Adverse effects	Contraindications/ Cautions	Recommended condition
Nicardipine	2nd generation dihydropyridine calcium channel blocker, arterial vasodilator	**O** : 5-15 min **D** : 2-6 hours	Tachycardia, flusing, headache, nausea, local phlebitis	Contraindicated in aortic stenosis Caution with cardiac ischemia and acute heart failure	Acute pulmonary edema,[3] hypertensive encephalopathy, acute renal failure, sympathetic crisis, acute ischemic stroke, acute postoperative hypertension
Labetalol	Alpha-1 and nonselective beta adrenergic antagonist	**O** : 5-10 min **D** : 2-6 hours	Bradycardia, bronchospam, nausea / vomiting, heart block	Avoid in patients with severe reactive airways disease or COPD, acute systolic heart failure, bradycardia, heart block or hepatic dysfunction	Acute pulmonary edema,[1] hypertensive encephalopathy, acute myocardial ischemia,[2] acute aortic dissection, acute postoperative hypertension,

					eclampsia, ischemic stroke
Esmolol	Cardioselective beta 1-adrenergic antagonist	**O** : 1-2 min **D** : 10-30 min	Bradycardia, nausea, bronchospasm heart block	Avoid in patients with severe reactive airways disease or COPD, acute systolic heart failure, bradycardia, heart block or hepatic dysfunction; Clearance not dependent on renal or hepatic function	Acute pulmonary edema,[1] acute myocardial ischemia,[2] acute aortic dissection, acute postoperative hypertension
Enalapril	Angiotensin-converting enzyme inhibitors	**O** : 15-30 min **D** : 12-24 hours	Angioedema, Diarrhea; dizziness or lightheadedness when sitting up or standing; headache; nausea; persistent, dry cough; tiredness; vomiting.	Contraindicated in patient with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema	

1 Associated with diastolic dysfunction.
2 In combination with intravenous nitroglycerin.
3 Associated with systolic dysfunction.

Table 3. Parenteral antihypertensive agent used in intracerebral hemorrhage stroke which can be used as alternative therapy

Agent	Mechanism of action	Onset and duration	Adverse effects	Contraindications/ Cautions	Recommended condition
Sodium Nitroprusside	Nitric oxide donor; vasodilates arteriolar and venous smooth muscle	**O** : immediate **D** : 1-2 min	Thiocyanate and cyanide toxicity, nausea/vomiting, headache, muscle spasm	Contraindicated in high output cardiac failure and pregnancy Caution use with renal disease, anemia, liver	Acute pulmonary edema, acute aortic dissection

				disease myocardial ischemia and increased intracranial pressure	
Hydralazine	Peripheral vasodilator that causes relaxation of arteriolar smooth muscle	**O** : 10-20 min **D** : 1-4 hours	Diarrhea; headache; loss of appetite; nausea; vomiting; Severe allergic reactions	contraindicated in hypersensitivity to Hydralazine, coronary artery disease, mitral valvular rheumatic heart disease	Eclampsia or preeclampsia
Nitroglycerine	Nitric oxide donor; venodilator	**O** : 2-5 min **D** : 5-10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Contraindicated in angle closure glaucoma Caution when cerebral or renal perfusion compromised	Adjunct agent for acute pulmonary edema[1-3] and acute myocardial ischemia

1 Associated with diastolic dysfunction.
2 In combination with intravenous nitroglycerin.
3 Associated with systolic dysfunction.

Nicardipine, labetatol, esmolol and enalapril is a preffered antihypertensive agent which can be concidered as first-line agent to treat acute high blood pressure in intracerebral hemorrhage stroke. Sodium nitroprusside, hydralazine, nitroglycerine can be as preffered agent if a special condition present in ICH stroke patient which can seen in table 3. Sodium nitroprusside, hydralazine, nitroglycerine can be used to if there is a contraindication or spesific caution in use of nicardipine, labetalol, esmolol and enalapril. Management of acute increase of blood pressure in ICH patient should be an individual therapy. Selection of antihypertensive agent should be according to patient spesific condition and patient respon to the therapy.

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