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HYPERTENSION MANAGEMENT

Evidence Based Medicine Guideline

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Approved: 6/8/2001 Revision(s): 10/9/2009, 11/25/2015, 1/27/2018, 10/25/2023

SUMMARY
Hypertension is commonly encountered in the surgical patient. Although most commonly related to inadequate pain control, a variety of other etiologies for either systolic or diastolic hypertension may be seen. This guideline aims to provide an overview of the available agents as well as guidance on drug selection and dosing for the treatment of hypertension in surgical patient.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Antihypertensive medications should be administered to patients with hypertensive emergencies (SBP > 180 mmHg or DBP > 110 mmHg) and evidence of end-organ dysfunction in the ICU setting to prevent further end organ damage.**
  - **For hypertensive emergencies, lower the MAP 20-25% in the first 60 minutes with the perfusion of short-acting titratable anti-hypertensive agents to prevent target organ damage.**
  - **Vasodilator infusions should be titrated to mean arterial pressure (MAP) rather than systolic or diastolic blood pressure.**
  - **Underlying causes of perioperative hypertension (including pain, anxiety, agitation, or hypoxia) should be ruled out before administration of antihypertensive agents.**
  - **Esmolol is the drug of choice for heart rate control in patients with acute aortic dissection; additional anti-hypertensive agents may be necessary to reach target blood pressure (< 120 mmHg).**
  - **Empiric perioperative beta-blockade should only be administered to patients taking a beta-blocker prior to hospital admission.**
- **Level 3**
  - **Labetalol or nicardipine are the first line agents for intracranial hemorrhage-associated hypertension.**
  - **Clevedipine, esmolol, nicardipine, and nitroglycerin are the preferred agents for treatment of patients with acute perioperative hypertension and no prior history of hypertension.**
  - **Hydralazine should be used with caution in patients with elevated intracranial pressure. Please see the "Severe Traumatic Brain Injury" guideline for further details.**
  - **Hydralazine should be used with caution in patients with myocardial ischemia due to risk of reflex tachycardia resulting in increased cardiac output and myocardial oxygen demand.**
  - **Caution should be used when initiating beta-blocker therapy in patients without prior exposure.**

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Hypertension (HTN) is defined into two categories with stage 1 HTN defined as a systolic blood pressure (SBP) 130-139 mmHg or a diastolic blood pressure (DBP) 80-89 mmHg (1), and stage 2 HTN defined as SBP > 140 mm Hg or a DBP > 90 mm Hg (1.23) Pre-existing hypertension is present in two-thirds of all patients over 60 years of age (2). A hypertensive crisis may refer to either "hypertensive emergencies" or "hypertensive urgencies" (1,3). Hypertensive emergencies are defined as severe elevations of SBP $\geq$ 180 mmHg and/or DBP $\geq$ 110 mmHg plus the presence of end-organ dysfunction (such as neurologic changes, intracranial hemorrhage, myocardial ischemia, aortic dissection, eclampsia, etc…) requiring immediate reduction in blood pressure (1,3-4). In contrast, hypertensive urgencies have no associated end-organ dysfunction and require reduction over hours to days (1,3-4). Acute hypertensive emergencies, defined as bleeding, myocardial infarction, and cerebral ischemia, can complicate 5-35% of perioperative patients and increase mortality four-fold (5).

The acute management of isolated systolic, isolated diastolic or combined systolic and diastolic hypertension differs. Generally, diastolic hypertension is more clinically important and should be treated first. The primary determinants of SBP are left ventricular contractility, stroke volume, and great vessel compliance. The primary determinants of DBP are systemic vascular resistance (SVR), peripheral run-off, and diastolic time interval (heart rate). Coronary perfusion pressure is determined by the difference between DBP and pulmonary artery occlusion pressure (PAOP) (6).

Patients with a history of uncontrolled hypertension shift their cerebral and renal perfusion autoregulation to function at the higher blood pressure levels. Consequently, too rapid a decrease in blood pressure may result in hypoperfusion of the brain and the kidneys (3). Treatment of hypertension may also affect coronary perfusion pressure and over-aggressive reductions in blood pressure, especially DBP, may result in the development of myocardial ischemia (6,7).

Vasodilator infusions should be titrated to MAP as the dynamic response artifacts of intra-arterial pressure monitoring systems least affect this parameter (8). Patients with SBP > 180 mmHg and/or DBP >120 with evidence of new, progressive or worsening end-organ damage are considered hypertensive emergency and should be admitted to the ICU (9,23). In general, these patients' blood pressure should be reduced by no more than 25% during the first hour, then over the next 2-6 hours it may be lowered to 160/100-110 mmHg, then to normal goals after 24 to 48 hours. A particular subset of these patients (those with aortic dissection, severe pre-eclampsia, or pheochromocytoma crisis) should be reduced to SBP < 140 mmHg in the first hour and < 120 mmHg for patients with aortic dissection (9,1,23).

While this remains true as a general statement, specific goals for perioperative BP should be tempered by patient's individual history, history of hypertension, and general condition. A general goal would be to keep the patient's blood pressure within 20% of perioperative values (9). Patients with SBP > 180 mmHg and/or DBP > 120 mmHg without evidence of end-organ damage may be initiated on, resume previous or increase current oral anti-hypertensive regimens.

Within the surgical population, there are two major principles of therapy for the management of hypertension (5):

1. Patients with a history of hypertension should be continued on their home antihypertensive therapy as soon as possible after admission to the hospital to minimize the development of rebound hypertension.
2. Acute hypertension in the postoperative period, in the absence of prior history, is almost always related to pain, anxiety, agitation, or abnormalities of gas exchange or pH.

ANTIHYPERTENSIVE MEDICATION REVIEW

Angiotensin Converting Enzyme (ACE) Inhibitors: captopril, enalapril, lisinopril, and others

ACE inhibitors block the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulator of aldosterone secretion. ACE inhibitors also block the degradation of bradykinin and stimulate the synthesis of other vasodilating substances including prostaglandin E2 and prostacyclin. The major hemodynamic effect of ACE inhibitors is decreased SVR due to increased compliance of large arteries. Enalaprilat, prodrug of enalapril, is the only ACE inhibitor available for intravenous administration. Adverse effects associated with the ACE inhibitors include dry cough, the development of angioedema, and a decline in renal function in patients with renal artery stenosis due to loss of the afferent-efferent pressure gradient with the blockade of angiotensin II (10-13).

Beta-Blockers: labetalol, metoprolol, esmolol, and others

There are several different proposed mechanisms for the antihypertensive effects of the beta-blocker class. First, beta-blockers lower cardiac output through negative chronotropic and inotropic effects on the heart. Second, non-selective beta-blocker agents, such as propranolol, exert action at both beta-1 and beta-2 receptors – activity at peripheral beta-2 receptors results in peripheral vasodilatation. Third, mixed agents such as labetalol, provide alpha-1, beta-1, and beta-2 blockade with both alpha-1 and beta-2 blockade leading to peripheral vasodilatation. Of all the beta-blockers, labetalol exerts the greatest effects on blood pressure due to the alpha-1 antagonism. Major adverse events associated with beta-blocker administration include bradycardia and AV conduction abnormalities. In comparison, esmolol is a selective beta-1 antagonist often used as an anti-arrhythmic and to treat rapid ventricular rates but is also commonly used off-label for treatment of hypertension and to lower heart rate in aortic dissection (10-12).

Calcium Channel Blockers (CCB): amlodipine, clevidipine, nicardipine, diltiazem, and others

CCBs cause relaxation of cardiac and smooth muscle by blocking voltage sensitive calcium channels thereby reducing the entry of extracellular calcium into the cells. Vascular smooth muscle relaxation leads to vasodilatation and a reduction in blood pressure. CCBs are classified as dihydropyridines and non-dihydropyridines. Dihydropyridines produce more peripheral vasodilatation compared to the non-dihydropyridines (including verapamil and diltiazem) which preferentially slow atrio-ventricular conduction. Clevidipine, the newest dihydropyridine CCB, is an arterial-selective vasodilator with subsequent systemic, pulmonary, and coronary vasodilatation (16). It has been primarily studied in the pre- and post-cardiac surgery population. Nicardipine, another dihydropyridine CCB, has both arterial and venous vasodilatory properties, including cerebrovascular smooth muscle. Unlike clevidipine, nicardipine also has an oral formulation which facilitates conversion from the continuous infusion (11-16).

Central Alpha-2 Agonist: clonidine

Clonidine stimulates alpha-2 adrenergic receptors in the brain leading to a reduction in sympathetic outflow from the vasomotor center and an associated increase in vagal tone. Because of the reduced sympathetic activity and some enhancement of parasympathetic activity, heart rate, CO, SVR and renin are decreased. In addition, baroreceptor reflexes are blunted. Adverse effects include sodium and fluid retention, rebound hypertension with abrupt withdrawal, sedation, and dry mouth (11-12).

Direct Vasodilators: sodium nitroprusside (SNP) and nitroglycerin (NTG)

Both SNP and NTG have direct effects on both venous and arterial smooth muscle resulting in smooth muscle relaxation and vasodilatation. While SNP exerts this effect equally, NTG has a greater effect on venous tone. Hemodynamic effects include afterload reduction (decreased SVR) and increased cardiac output (CO) in the presence of adequate preload. Preload reduction occurs due to a decrease in venous tone and reduced aortic and left ventricular impedance. It is important to remember that SNP is metabolized to cyanide and thiocyanate. Hepatic and/or renal failure can lead to accumulation of these breakdown products and the development of cyanide toxicity (3,11,12).

Dopaminergic (D1) Agonist: fenoldopam

Fenoldopam is a post-synaptic dopaminergic (D1) agonist leading to vasodilatation of peripheral arteries, renal and mesenteric vasculature. Fenoldopam lowers systemic blood pressure and peripheral vascular resistance while maintaining renal perfusion. Fenoldopam may raise intraocular pressure and intracranial pressure and should be avoided in patients with glaucoma or elevated intracranial pressure (3,10).

Peripheral Vasodilators: hydralazine and minoxidil

Similar to SNP, minoxidil causes venous and arterial smooth muscle relaxation. Hydralazine, however, is a direct arterial vasodilator and affects DBP more than SBP. Both minoxidil and hydralazine cause a decrease in SVR and subsequent reflexive tachycardia which frequently requires concomitant beta-blocker administration (3,10,17).

Peripheral Alpha-1 Blockers: doxazocin, prazocin, and terazocin

Peripheral alpha-1 blockade leads to arterial and venous vasodilatation resulting in decreased SVR and reflex tachycardia. Adverse effects include sodium and fluid retention as well as vivid dreams and depression. Additionally, these drugs exert a so-called “first-dose phenomenon” characterized by transient dizziness or faintness, palpitations, and syncope within one to three hours after the first dose. Adverse events associated with these agents can be minimized by dosing at bedtime (10-11).

LITERATURE REVIEW

There have been numerous studies conducted with the various anti-hypertensive agents. The type of agent chosen depends on several patient factors including age, race, pregnancy status, volume status, and the presence of end-organ disease or compromise (1). There is limited data for many of the uses of antihypertensives in the ICU. This guideline attempts to provide recommendations for some of the more common surgical critical care indications.

In 1999, Perez et al. reviewed the use of esmolol and sodium nitroprusside at their institution for heart rate (HR) and blood pressure (BP) control during transport of patients with acute aortic dissections. They conducted two separate retrospective reviews (n=119 for the first study and n-151 in the second study). Both studies found a higher percentage of patients achieved target BP and HR treated by a standardized protocol than without it (18). [Class II]

The POISE study group conducted a prospective, randomized trial comparing the effects of extended-release metoprolol 100 mg po with placebo on 30-day risk of major cardiovascular events in patients undergoing non-cardiac surgery. They enrolled 8,351 patients in the trial (4,174 in the metoprolol group and 4,177 in the placebo group). The primary outcome was the composite of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal cardiac arrest at 30 days after enrollment. The authors did identify a statistically significant decrease in overall cardiovascular events ($p=0.04$), this was due largely to significantly fewer myocardial infarctions ($p=0.0017$) in the metoprolol group. However, patients in the metoprolol group had significantly more strokes, there was a higher rate of mortality and more episodes of sepsis in the metoprolol group compared to placebo ($p<0.05$). The authors identified clinically significant hypotension as the major risk factor for the development of stroke or death (19). [Class I]

In contrast to the positive results of the POISE trial the MaVS study randomized 496 patients to metoprolol or placebo 2 hours before surgery and continuing 5 days into the patient's hospital stay. It was found that intraoperative and postoperative bradycardia and hypotension requiring intervention were more frequent in the metoprolol group. While beta blockade has positive effects of blood pressure and tachycardia it can increase adverse effects of bradycardia and hypotension, especially in those who are beta-blocker naïve (20).

The side effects of anti-hypertensive agents can limit their usage. The first adverse effect is a transient increase in intracranial pressure that could be detrimental to those with increased intracranial pressure. A study in 1975 enrolled six patients whose intracranial pressure was measured when given hydralazine. There was an increase in ICP by 110% before a 20% decrease in BP. This is thought to be due to a pronounced effect upon cerebral capacitance vessels more so than cerebral resistance vessels. Paradoxically, overall cerebral blood flow (CBF) increases. In patients who have increased ICP, the use of hydralazine should be considered with caution (21). The second adverse effect of hydralazine is related to its risk of reflex tachycardia. This leads to increased cardiac output and concomitant increase in myocardial oxygen demand. In patients at risk of myocardial ischemia, this could lead to myocardial infarction (22).

One of the more recent landmark studies on hypertension was the systolic blood pressure intervention trial (SPRINT) in 2015. In this study, 9,361 patients who were at high risk for cardiovascular events without diabetes were randomized to an intensive treatment group of a SBP goal <120 mmHg versus a treatment goal of <140 mmHg. The trial was stopped early after 3.26 years after it was found that the intensive treatment group had significantly lower rates of cardiovascular events and death from any cause. However, the intensive group was found to have a significantly higher rate of adverse events (24).

Studies have failed to prove that any medication is superior in the treatment of hypertension in the acute setting. There is also controversy as to the target BP goal. However, most major societies (American Heart Association, American College of Cardiologists) agree, as proven by multiple studies, that SBP >180 mmHg should be treated aggressively in the setting of hypertensive emergency (23).

REFERENCES

1. National Heart Lung and Blood Institute. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. www.nhlb.nih.gov/guidelines/hypertension/jnc7full.pdf. [Accessed 06-Oct-2009].
2. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk of developing hypertension in middle-aged women and men: the Framingham Heart Study *JAMA* 2002; 287: 1003-10.
3. Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies, part 1. *Am J Health-Syst Pharm* 2009; 66(1):1343-1352.
4. Varon J, Marik PE. Perioperative hypertension management. *Vasc Health Risk Manag* 2008; 4(3):615-627.
5. Gal TJ, Cooperman LH; Hypertension in the Immediate Postoperative Period. *Br J Anesth* 1975; 47:70-74.
6. Morgan GE, Jr., Mikhail MS, Murray MJ, "Chapter 19. Cardiovascular Physiology & Anesthesia" (Chapter). Morgan GE, Jr., Mikhail MS, Murray MJ: *Clinical Anesthesiology*, 4e: http://www.accessmedicine.com.lp.hscl.ufl.edu/content.aspx?aID=889833. [Accessed 06-Oct-2009]
7. Katzung Bertram G, Chatterjee Kanu, "Chapter 12. Vasodilators & the Treatment of Angina Pectoris" (Chapter). Katzung BG: *Basic & Clinical Pharmacology*, 11e: http://www.accessmedicine.com.lp.hscl.ufl.edu/content.aspx?aID=4518124. [Accessed 06-Oct-2009].
8. Mohrman DE, Heller LJ, "Chapter 6. The Peripheral Vascular System" (Chapter). Mohrman DE, Heller LJ: *Cardiovascular Physiology*, 6e: http://www.accessmedicine.com.lp.hscl.ufl.edu/content.aspx?aID=2373081. [Accessed 06-Oct-2009].
9. Dodson GM, Bentley WE, Awad A, et al. Isolated Perioperative hypertension: clinical implications and contemporary treatment strategies. *Curr Hypertens Rev* 2014; 10(1):31-36.
10. Lexi-Comp Online. © 2009. [Accessed 06-Oct-2009]
11. Micromedex Healthcare Series. © 2009. [Accessed 06-Oct-2009].
12. Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies, part 2. *Am J Health-Syst Pharm* 2009; 66:1448-1457.
13. Package Insert: Enalaprilat sodium injection. © 2004.
14. Package Insert: Nicardipine hydrochloride (Cardene®). © 2007.
15. Package Insert: Clevidipine butyrate injectable emulsion (CleviprexTM). © 2009.
16. Cada DJ, Levien TL, Baker DE. Clevidipine butyrate injectable emulsion. *Hosp Pharm* 43(11):903-912.
17. Ram CVS, Fenves A. Clinical pharmacology of antihypertensive drugs. *Cardiol Clin* 2002; 20(2):265-280.
18. Perez L, Wise L. A standardized treatment protocol for blood pressure management in transport patients with a reported diagnosis of acute aortic dissection or symptomatic aortic aneurysm. *Air Med J* 1999; 18(3):111-113.
19. POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomized controlled trial. *Lancet* 2008; 371:1839-1847.
20. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006; 152:983–990.
21. Overgaard J, Skinhoj E. A paradoxical cerebral hemodynamic effect of hydralazine. Stroke 1975; 6:402-404.
22. Powers DR, Papadakos PJ, Wallin JD. 1998. Parenteral hydralazine revisited. *J Emerg Med* 16:191-196.
23. Whelton PK, Carey RM, Aronow WS, et al.. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Am J Coll Cardiol 2017; 71:e127-248.
24. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *NEJM* 2015: 373:2103-2116.