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REVIEW-SYSTEMATIC

Management of Perioperative Hypertensive Urgencies With Parenteral Medications

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BACKGROUND: Hypertension is the major risk factor for cardiovascular (CV) disease such as myocardial infarction (MI) and stroke. This risk is well known to extend into the perioperative period. Although most perioperative hypertension can be managed with the patient's outpatient regimen, there are situations in which oral medications cannot be administered and parenteral medications become necessary. They include postoperative nil per os status, severe pancreatitis, and mechanical ventilation. This article reviews the management of perioperative hypertensive urgency with parenteral medications.
METHODS: A PubMed search was conducted by cross-referencing the terms "perioperative hypertension," "hypertensive urgency," "hypertensive emergency," "parenteral anti-hypertensive," and "medication." The search was limited to English-language articles published between 1970 and 2008. Subsequent PubMed searches were performed to clarify data from the initial search.
RESULTS: As patients with hypertensive urgency are not at great risk for target-organ damage (TOD), continuous infusions that require intensive care unit (ICU) monitoring and intraarterial catheters seem to be unnecessary and a possible misuse of resources.
CONCLUSIONS: When oral therapy cannot be administered, patients with hypertensive urgency can have their blood pressure (BP) reduced with hydralazine, enalaprilat, metoprolol, or labetalol. Due to the scarcity of comparative trials looking at clinically significant outcomes, the medication should be chosen based on comorbidity, efficacy, toxicity, and cost. ***Journal of Hospital Medicine*** **2010;5:E11–E16.** © *2010 Society of Hospital Medicine.*

KEYWORDS: **hypertension, hypertensive urgency, operative, parenteral, surgery.**

An association between hypertension and operative risk has been reported in small studies since the early 1970s. In two studies, Prys-Roberts et al.[1,2] found that subjects with uncontrolled hypertension were more likely to have myocardial ischemic changes on electrocardiography with episodes of hypotension during induction of anesthesia. Subjects without hypertension or with hypertension controlled by medication were less likely to have episodes of hypotension, regardless of the type of anesthetic.

Hypertension increases the risk of developing perioperative heart failure (HF), renal failure, myocardial ischemia, or stroke. The level of risk is dependent upon the blood pressure (BP) level. It has been shown that a BP of <180/110 mm Hg without target-organ damage (TOD) is not an independent risk factor for perioperative cardiovascular (CV) complications, suggesting this level of BP does not need to be reduced rapidly to normal.[3,4]

The Joint National Committee defines hypertensive emergency as severe elevations in BP (usually >180/120 mm Hg) that produce evidence of TOD.[5] Patients with this level of BP who are asymptomatic and have no signs of TOD are considered to have hypertensive urgency. As patients with this level of BP are at higher risk perioperatively, pharmacotherapy is indicated. When oral medications cannot be administered, hypertensive urgency can be managed with a parenteral medication. The agent should be easily and predictably titrated, safe, and convenient (Table 1). This article reviews the management of perioperative hypertensive urgency with parenteral medications. The management of hypertensive emergencies, aortic dissection, and hypertension of pregnancy is outside the scope of this review.

Preoperative Considerations

In normotensive patients the induction of anesthesia can cause an acute elevation in BP (20–30 mm Hg) and heart rate (HR) (15–20 bpm).[6] In patients with preexisting hypertension these changes are often greater, with elevations up to 90 mm Hg and 40 bpm. As anesthesia progresses systolic BP starts to fall (−30 mm Hg), as a direct effect of both the anesthetic and the inhibition of the sympathetic nervous system (SNS). Patients with uncontrolled hypertension can have more severe reductions (−60 mm Hg).[6] This can result in intraoperative hypotension and shock. In a study of over 650 patients, marked intraoperative hypotension (<50% of preoperative BP or a 33% reduction for more than 10 minutes) was an independent risk factor for perioperative CV complications (cardiac arrhythmia, ischemia, HF, or renal failure).[7]

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TABLE 1. Parenteral Drugs for Treatment of Hypertension

Drug	Dose	Onset of Action	Duration	Use With Caution in	Adverse Reactions	Pregnancy Class*	Daily Cost†
Hydralazine hydrochloride	10–20 mg IV q4–6h	10–20 minutes	1–4 hours	Increased ICP; aortic dissection; myocardial ischemia	Reflex tachycardia; headache, flushing, vomiting	C	20 mg q4h, $90
Metoprolol	1.25–5.0 mg IV q6h	20 minutes	5–8 hours	Heart block; bradycardia; acute heart failure	Bronchospasm	C (first trimester); D (second-third trimesters)	5 mg q6h, $10
Enalaprilat	1.25–5.0 mg IV q6h	15–30 minutes	6–12 hours	Hyperkalemia; acute renal failure; hypovolemia	Hypotension; angioedema	C (first trimester); D (second-third trimesters)	5 mg q6h, $60
Labetalol hydrochloride	20–80 mg IV q10min (max 300 mg daily)	5–10 minutes	3–6 hours	See metoprolol	Bronchospasm; nausea, vomitting; scalp tingling	C (first trimester); D (second-third trimesters)	300 mg, $15
Transdermal clonidine	0.1–0.3 mg once weekly	2–3 days	7 days	Abrupt withdrawal‡; elderly	Drowsiness, dizziness; local skin erythema; dry mouth	C	0.3 mg/24-hour patch, $10

Abbreviations: IV, intravenously; q, every; ICP, intracranial pressure.

*Pregnancy class: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk can not be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.

† Cost based on maximum recommended dose for 24 hours at average wholesale price (AWP) as listed in Red Book: Pharmacy's Fundamental Reference®. 111th edition. New York: Thomson Healthcare, 2007.

‡ If taking oral clonidine preoperatively, it is necessary to switch to transdermal preparation at least 3 days prior to avoid rebound hypertension.

Therefore, when BP is mildly elevated at the time of surgery (<180/110 mm Hg), rapid reduction in BP is not necessary, and studies have been unable to demonstrate a benefit to delaying surgery.[8] However, when BP is ≥180/110 mm Hg preoperatively, antihypertensive medications should be administered and intraoperative blood pressure monitored closely. There is a lack of data to support delay of surgery.[9]

Postoperative Considerations

The postoperative period is also associated with elevations in BP. In the immediate recovery phase from anesthesia, there is a mild elevation in BP within 10 to 15 mm Hg, but there are larger fluctuations in patients with preexisting hypertension.[6] Otherwise postoperative hypertension can be seen from a variety of causes such as pain, excitement on emergence from anesthesia, and hypercarbia.[10] Less common causes include agitation, hypoxemia, and hypervolemia. These secondary causes should be identified and treated before any antihypertensive medications are administered.

Drug Therapy

When evaluating a patient with a BP of ≥180/110 mm Hg, the physician must first classify the patient as having a hypertensive emergency or urgency. Hypertensive emergencies require immediate reduction in BP to prevent or limit hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction (MI), HF and aortic dissection.[11] This is often accomplished by using continuous infusions of medications such as nitroprusside, nicardipine, or fenoldopam, and requires monitoring in an intensive care unit (ICU) with an intraarterial catheter.

As patients with hypertensive urgency are not at great risk for TOD, continuous infusions of the above medications that require ICU monitoring and intraarterial catheters seem to be unnecessary, and a possible misuse of resources. Treating hypertensive urgency in this manner could also be potentially dangerous.[12,13] Patients with chronic hypertension often have autoregulation of organ perfusion shifted to a higher range of mean arterial pressure, so excessive pressure reductions to "normal" BP values may induce organ hypoperfusion.[14] Therefore, BP in hypertensive urgency can be lowered to ≤160/100 mm Hg over time.[5] When oral medications cannot be used, there are several parenteral agents.

Diltiazem Hydrochloride and Verapamil

Diltiazem hydrochloride and verapamil are non-dihydropyridine calcium-channel blockers that produce vasodilation by decreasing calcium entry into vascular smooth muscle. In a study of 18 hypertensive patients, administration of intravenous diltiazem resulted in significant BP reductions within 5 minutes, however a variety of rhythm disturbances and heart block (HB) were observed.[15] Verapamil has also been shown to successfully lower BP.[16] However, when given at antihypertensive doses, verapamil has been shown to cause prolongation of the PR interval (30%), second-degree block (0.7%), and complete HB (1.7%).[17]

Therefore, although oral diltiazem and verapamil may be appropriate for treating hypertension, the intravenous formulations are indicated only for the treatment of atrial fibrillation or flutter, and paroxysmal supraventricular tachycardia.[18]

Clonidine

Clonidine stimulates alpha$_2$-adrenoreceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system, and decreases in peripheral resistance, renal vascular resistance, HR, and BP. Renal blood flow and glomerular filtration rate remain essentially

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unchanged. Normal postural reflexes are intact; therefore, orthostatic symptoms are mild and infrequent. Sudden cessation of treatment with clonidine has been associated with dangerous rebound hypertension.

Catapres-TTS (clonidine) transdermal releases clonidine at a constant rate for 7 days. Therapeutic levels are achieved 2 to 3 days after initial application. After removal, therapeutic levels persist for about 8 hours and decline slowly over several days.[19]

Perioperatively, beneficial effects of clonidine include decreased anesthetic and opioid requirements, reduced hemodynamic responses to intubation and other stimuli, and improved postoperative renal function.[20] Alpha$_2$ agonists have also been shown to have significant antiischemic properties.[21,22]

Beta-adrenoreceptor (β) Blockers

Beta blockers are of particular interest in the management of perioperative hypertension. Several studies in the 1980s demonstrated that preoperative use of β-blockers attenuated the severe BP fluctuations in the perioperative period; there was also a reduction in myocardial ischemia.[21–24] In addition, the preoperative β-blockers in select at-risk populations has been shown to decrease the rate of CV events (MI, unstable angina, need for coronary-artery bypass, HF) and death.[25,26]

Given these findings, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the perioperative CV evaluation and care for noncardiac surgery recommended β-blockers in patients receiving β-blockers for angina, symptomatic arrhythmias, or hypertension; those undergoing vascular surgery with coronary artery disease or a revised cardiac risk index (RCRI) score >1; and those undergoing intermediate risk surgery with a RCRI of >1.[27,28] However, the recently published Perioperative Ischemic Evaluation Study (POISE) trial demonstrated that while β-blockers reduced the risk of perioperative MI, there was an overall increase in net mortality.[29] Given that most of the patients had an RCRI of 1 to 2, the ACC/AHA plans to revise this guideline.

If a β-blocker is selected to manage perioperative hypertension, there are two available for parenteral use.

Metoprolol Tartrate

Metoprolol is a β-$_1$ selective adrenoreceptor antagonist available in both oral and intravenous formulations. Acutely, it decreases cardiac output by reducing both HR and contractility, therefore resulting in a decrease in BP. Over the course of a week it antagonizes β-receptors in the juxtaglomerular complex, suppressing renin release and therefore production of angiotensin II.[30] Metoprolol may lower BP by other mechanisms, including alteration of the sympathetic nervous system (SNS) and altered baroreceptor sensitivity.

The oral formulation is most commonly used to treat hypertension, MI, angina, atrial fibrillation, and HF. The intravenous form is only approved for the treatment of acute MI and supraventricular tachycardia. However, intravenous administration does induce its maximal hypotensive response within 20 minutes, generally lasting 3 to 4 hours. In a study investigating metoprolol and perioperative hypertension during extubation, the administration of intravenous metoprolol safely blunted the expected rise in BP.[31] Similar findings were demonstrated in neurosurgical patients.[32]

Even though intravenous metoprolol can effectively lower BP, it does so mainly by reducing cardiac output. Therefore, caution must be taken in patients with a low cardiac index, and it should be avoided in acute HF, bradycardia or greater than first-degree HB, or bronchospasm.

As metoprolol is a far more commonly used substitute for atenolol, we have deferred its specific discussion.

Labetalol Hydrochloride

Labetalol antagonizes both alpha$_1$- and nonselective β-adrenoreceptors. When given intravenously the onset of action is 5 minutes, but the duration can vary from 20 minutes to 23 hours, with an average of generally 6 hours. An initial dosage of 10 to 20 mg administered over 2 minutes can be followed by repeat doses every 10 minutes until the desired BP goal is achieved (maximum 300 mg daily). It decreases systemic vascular resistance and typically has no significant effect on cardiac index. In a multicenter study, bolus doses produced a rapid, smooth reduction in BP without reflex tachycardia or serious side effects.[33] It has been shown to have similar efficacy and safety in cardiac surgery and other surgery requiring anesthesia.[34,35] Furthermore, it does not increase intracranial pressure,[36] and is safe in patients with renal insufficiency or pregnancy. Contraindications to labetalol are hypotension, bradycardia, high-degree HB, and severe asthma or chronic obstructive pulmonary disease.

Hydralazine Hydrochloride

Hydralazine reduces BP by increasing cyclic-guanosine monophosphate in vascular smooth muscle, therefore leading to direct arterial vasodilation with little effect on venous circulation.[37] It causes rapid reductions in BP, sometimes resulting in reflex tachycardia. When given intravenously, it has an onset of action of 5 minutes and duration of 3 to 8 hours, dependent mostly on hepatic clearance. This variability in hepatic acetylation and inactivation leads to some difficulty in drug titration.[38] The starting dose is usually 10 mg, and it is administered every 4 to 6 hours. As stated, intravenous administration results in an increase in HR, cardiac output, myocardial contractility, and an overall increase in sympathetic activity.[39]

Although hydralazine has been used for the management of perioperative hypertension for several decades,[40] its overall efficacy and safety have not been adequately defined for this setting. It has proven to be most successful during hypertension in pregnancy[41] or hypertensive emergency.[42] However, hydralazine is still widely used and is considered

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by some experts as an acceptable antihypertensive drug in the perioperative setting, as it can be administered in divided doses, routinely at 4 to 6 hour intervals, making it suitable for the treatment of hypertension in subjects unable to take medications by mouth or when a continuous infusion is unnecessary.

Hydralazine should be used with extreme caution in patients with evidence of cardiac ischemia, and it should be avoided in patients with aortic dissection or an increased intracranial pressure. The activation of the SNS and arterial vasodilation could have a potential benefit for patients with renal dysfunction.

Enalaprilat

Enalaprilat is the intravenous preparation of the active form of the angiotensin converting enzyme (ACE) inhibitor enalapril. By ACE inhibition, enalaprilat leads to a reduction in the production of angiotensin II, thereby reducing mean arterial pressure. The usual dose is 1.25 mg, and as much as 5 mg may be given every 6 hours as necessary,[43] making it suitable for the treatment of hypertension in subjects unable to take medications by mouth.

Enalaprilat has demonstrated efficacy and safety when used in both CV surgery and neurosurgery. In a study of 14 patients with chronic HF, the administration of enalaprilat resulted in significant reductions in both mean arterial pressure (−21%) and pulmonary capillary wedge pressure (−33%).[44] There was also an increase in the stroke volume index (20%) without a change in coronary blood flow or myocardial oxygen consumption, indicating an improvement in left ventricular function. As ACE inhibitors do not impair cerebral blood flow, enalaprilat may also be used safely in neurosurgery.[45] Additionally, enalaprilat has been studied in the treatment of hypertensive urgencies. In a study of patients who had a diastolic BP between 100 and 114 mm Hg, the administration of 1.25 mg of enalaprilat lead to a significant reduction in systolic and diastolic BP within 60 minutes without any major adverse events.[46]

Even though enalaprilat has demonstrated safety and efficacy in several perioperative trials, its actions may be variable and not always predictable. When investigating the appropriate dose of enalaprilat, Hirschl et al.[43] randomized 65 patients to receive different doses of enalaprilat. Response to treatment was defined as a stable reduction in BP to 180/95 mm Hg within 45 minutes. The goal was reached in only 63%, and surprisingly the response rates did not differ across differing dosages: 0.625 mg (67%), 1.25 mg (65%), 2.5 mg (59%), and 5 mg (62%).

Continuing chronic ACE inhibitor therapy within 12 to 24 hours preoperatively has been associated with severe hypotension at or shortly after induction of anesthesia. In a recent meta-analysis, Rosenman et al.[47] assessed the clinical consequences of preoperatively continuing vs. withholding ACE inhibitors or a angiotensin II receptor blocker (ARB) in patients treated chronically with these agents. Patients receiving an immediate preoperative ACE inhibitor or ARB were significantly more likely to develop hypotension requiring vasopressors. Although this observation cannot be directly translated, caution should be advised when selecting intravenous enalaprilat for the acute lowering of BP preoperatively.

Enalaprilat is contraindicated in pregnancy and patients with bilateral renal artery stenosis. It must also be used carefully in patients with hyperkalemia, acute renal failure, or hypovolemia.[48] There should also be a dose adjustment when given to patients with severe chronic kidney disease.[49] In addition, its use 12 to 24 hours prior to the induction of anesthesia should be discussed with the anesthesiologist.

Discussion

Nitroprusside, nitroglycerin, nicardipine, and fenoldopam are all effective antihypertensive medications. However, their availability only as continuous infusions requires ICU monitoring and an intraarterial catheter, and they are therefore unnecessary in the management of hypertensive urgency. The parenteral medications that do not require a continuous infusion are diltiazem, verapamil, metoprolol, labetalol, enalaprilat, hydralazine, and transdermal clonidine.

As stated, the intravenous formulations of diltiazem and verapamil are indicated only for certain arrhythmias. Because the onset of action of transdermal clonidine is about 2 days and the offset is 8 hours, it has limited usefulness in the treatment of perioperative hypertension. Therefore, only metoprolol, labetalol, enalaprilat, and hydralazine have a major role in the treatment of hypertensive urgency when oral medications cannot be used.

When given intravenously, enalaprilat and hydralazine are safe, effective, widely available, and inexpensive. When deciding between these 2 agents, a few other considerations may be of importance. Even though ACE inhibitors have well-recognized benefits in the management of HF[50] and diabetic nephropathy,[51] these characteristics are not relevant in the short-term use of enalaprilat to treat perioperative hypertension. However, enalaprilat may be preferred over hydralazine when activation of the SNS and reflex tachycardia is to be avoided (cardiac ischemia, aortic dissection, increased intracranial pressure). Hydralazine may be preferred in the setting of hyperkalemia and acute renal failure. It must be preferred in pregnancy or bilateral renal artery stenosis.

Although the weight of the evidence of perioperative β-blocker use to reduce CV events in noncardiac surgery suggests a benefit, there are significant limitations. Few studies have compared different β-blockers. Studies to determine the ideal target population, duration of therapy, and route of administration are lacking. Additionally, using perioperative β-blockers may cause harm in low-risk patients.[52] Care should be taken when using labetalol and metoprolol in combination as they can induce a dangerous reduction in

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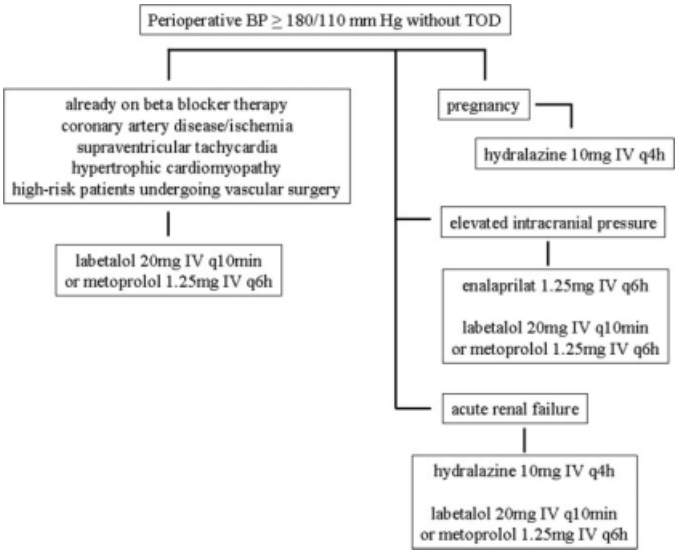

FIGURE 1. Algorithm for the management of perioperative hypertension with parenteral medications. TOD, target-organ damage.

HR. The role of acute administration of intravenous β-blockers in the setting of myocardial ischemia is debatable, and probably dangerous in the setting of hypotension, bradycardia, HB, pulmonary edema, or bronchospasm.[53]

Therefore, generalizing the perioperative β-blocker data to all patients with perioperative hypertension seems unlikely to have significant benefit, and may possibly pose harm.[29] However, it seems reasonable to use β-blockers in those in whom it would be indicated otherwise, and to continue parenteral therapy in those already taking a β-blocker preoperatively in order to avoid withdrawal.[54]

When deciding between metoprolol and labetalol, a few considerations may be of importance. First, there is much more evidence documenting the safety and efficacy of labetalol in perioperative hypertension. Second, even though metoprolol has proven benefit in patients with chronic HF, coronary artery disease (CAD), and MI, these long-term studies investigated oral metoprolol, not the intravenous formulation.[55] Most importantly, labetalol is more effective at lowering BP due to its additional blockade of alpha$_1$ adrenoreceptors. Neither drug should be used in acute HF, bradycardia or greater than first-degree HB, or bronchospasm. In conclusion, intravenous labetalol should be preferred over intravenous metoprolol for the management of perioperative hypertension.

Conclusions

Perioperative hypertension ideally should be evaluated well before the operative time period, when there is adequate time to initiate medications. Secondary causes such as pain, agitation, hypercarbia, hypoxemia, and hypervolemia should be treated directly prior to the administration of antihypertensive medications. It is uncertain whether patients with a BP of <180/110 mm Hg benefit from any specific parenteral medication, as there is little evidence from several studies that this level of BP without TOD leads to an increase in perioperative morbidity or mortality.[3,4,7,56] However, patients with hypertensive urgency are at higher risk for perioperative complications; therefore, their BP should be managed gradually to <160/110 mm Hg with the outlined recommended parenteral regimen (Figure 1).

When selecting a parenteral medication, we suggest first to exclude any contraindications, or see if an indication exists for a specific agent. Hydralazine, enalaprilat, metoprolol, or labetalol can be used as first-line agents. Due to the scarcity of comparative trials looking at clinically significant outcomes (length of hospital stay, morbidity, mortality), decisions for the management of perioperative hypertension should be made based on comorbidity, efficacy, toxicity, and cost (Table 1).

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