



Review article

Perioperative hypertension: a review of current and emerging therapeutic agents^{☆,☆☆}

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Abstract Perioperative hypertension is a common problem encountered by anesthesiologists, surgeons, internists, and intensivists. Surprisingly, no randomized, placebo-controlled studies exist that show that the treatment of perioperative hypertension reduces morbidity or mortality. Nevertheless, perioperative hypertension requires careful management. While sodium nitroprusside and nitroglycerin are commonly used to treat these conditions, these agents are less than ideal. Intravenous beta blockers and calcium channel blockers have particular appeal in this setting.

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1. Introduction

Hypertension is one of the most common chronic medical conditions in the United States, affecting close to 30% of the

population over the age of 20 years [1,2]. The prevalence of hypertension increases markedly with aging, affecting up to 60% to 70% of the population beyond the seventh decade of life [3,4]. The World Health Organization has estimated that by the year 2025, one third of the global population will be suffering from this illness.

Hypertension is a major risk factor for cardiovascular disease, stroke, and renal disease. It is now well established that treatment of hypertension reduces the risk of developing these conditions [5–9]. Furthermore, isolated systolic hypertension, which is particularly common in the elderly, is associated with an increased risk of cerebrovascular and coronary artery disease (CAD). Treatment of isolated systolic hypertension reduces the risk of these complications [10,11]. The most recent report from the Joint National Committee on Prevention, Detection, Evaluation, and

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Treatment of High Blood Pressure (JNC VII) recommends risk factor modification and treatment with antihypertensive agents in all patients with systolic blood pressure (SBP) greater than 140 mmHg and/or diastolic blood pressure (DBP) greater than 90 mmHg, regardless of age [2].

As chronic hypertension is extremely common in the general population, management of patients with hypertension undergoing surgery is of major clinical importance. Chronic hypertension increases complications and mortality following a wide spectrum of surgical procedures. This association was first suggested by Smithwick and Thompson who, in 1953, reported that the mortality of hypertensive patients undergoing sympathectomy was sixfold higher than for normotensive patients undergoing similar operations [12]. More recent data support the concept that patients with chronic hypertension are at increased risk of complications and death after surgery. The National Veterans Administration Surgical Risk study of 83,000 patients found that hypertension was the second most common risk factor for surgical morbidity [13]. Numerous other studies have confirmed this finding [14-22]. The association between chronic hypertension and increased perioperative complications in patients undergoing surgery is probably related to the fact that hypertension increases the risk of cardiovascular, cerebrovascular, and renal disease, and that these comorbidities increase the risk of surgery. It is not clear, however, that increased blood pressure (BP) *per se* increases surgical risk or that normalization of BP preoperatively reduces these risks. Overzealous BP control may result in unnecessary postponements of elective surgery and increase the risk of ischemic organ injury and adverse drug reactions.

The controversy regarding management of preoperative hypertension dates back to the study by Prys-Roberts and colleagues, published in 1971 [23]. This study compared three groups of patients: a control group consisting of 7 elderly normotensive patients with an average mean arterial pressure (MAP) of 89 mmHg, a group of 7 hypertensive patients whose elevated BP pressure was not being treated preoperatively and who had an average MAP of 129 mmHg, and a group of 15 hypertensive patients whose high BP was treated preoperatively and who had an average MAP of 129 mmHg. Patients with untreated hypertension had the greatest absolute decrease in BP and the highest percentage of arrhythmias and ischemic episodes. This study was non-randomized; there were major imbalances between groups with respect to type of surgery performed and severity of comorbidities. Furthermore, a standard anesthetic technique was used for all patients. This controversy is further fueled by the study of Goldman and Caldera, published in 1979 [16]. These investigators compared surgical outcomes in three groups of patients: sick hypertensive patients whose high BP was treated preoperatively, less sick hypertensive patients whose high BP was “undertreated” preoperatively, and less sick, only moderately hypertensive patients, who received no treatment preoperatively. No difference in outcome between groups was found.

Weksler et al. performed a “quasi”-randomized controlled study (RCT) in 989 chronically treated hypertensive patients who were scheduled for noncardiac surgery and who had a preoperative DBP of between 110 and 130 mmHg [24]. These investigators excluded patients with known CAD or cerebrovascular disease, left ventricular hypertrophy, valvular disease, or conduction defects. The control group had their surgery postponed and they remained in the hospital for BP control, while the study patients received 10 mg of nifedipine intranasally prior to surgery. There was no difference in postoperative complications between the two groups, which suggested that this subset of patients without significant cardiovascular comorbidity can proceed with surgery despite elevated BP on the day of surgery. The generalizability of these findings is limited because of the absence of neurologic or cardiovascular complications in either group, suggesting that it was a very low-risk population. However, the use of intranasal nifedipine in this study is worrisome (see below), and the number of patients in the treatment group who developed severe hypotension after administration of the nifedipine was not reported.

2. Perioperative beta blockers

In a “landmark” study published in 1996, Mangano et al. showed that perioperative administration of atenolol significantly reduced the rate of cardiac events and all cause mortality within six months of surgery in high risk patients undergoing non-cardiac surgery [25]. Seventy-one percent of patients in the atenolol group had a history of chronic hypertension. Based largely on the results of this study, the American College of Cardiology/American Heart Association recommend perioperative beta blockers for patients with established or risk factors for CAD or untreated hypertension, undergoing noncardiac surgery [26]. However, these recommendations have come under much scrutiny, as an intention-to-treat analysis of the Mangano et al. study showed no statistical difference between groups [27,28]. A meta-analysis investigating the use of beta blockers on perioperative outcome failed to show a significant beneficial effect on any of the individual outcome measures [29]. Furthermore, the Diabetes POstoperative Mortality and morbidity (DIPOM) trial failed to show a benefit of perioperative atenolol in diabetic patients undergoing major noncardiac surgery [30]. In addition, while previous trials and subgroup analysis suggested that patients undergoing vascular surgery may benefit from perioperative beta blockers [29,31-33], the Metoprolol after Vascular Surgery (MaVS) study was unable to show a reduction in the composite primary outcome or any individual outcome variable [34]. The recently published PeriOperative ISchemic Evaluation (POISE) trial showed that the perioperative use of extended-release metoprolol reduced the risk

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