Clevidipine’s Role In Perioperative Hypertension: The Escape And Eclipse Trials

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Learning Objectives:

1. Understand the evidence supporting the use of specific agents for treating perioperative hypertension.
2. Understand potential adverse effects of commonly used antihypertensive agents in surgical patients.
3. Understand the pharmacology and pharmacokinetics of clevidipine and other dihydropyridine calcium channel antagonists.

Background

The treatment of perioperative hypertension is widely considered the standard of care. However, until only recently, there have been few multi-centered randomized clinical trials to compare the safety and efficacy of specific pharmacologic agents for the treatment of perioperative hypertension. Early approaches to treatment with agents such as sodium nitroprusside or sublingual nifedipine were highly effective but raised significant safety concerns (1-3). To address these safety concerns, a multicenter trial was conducted comparing nicardipine to sodium nitroprusside that subsequently led to the approval of intravenous nicardipine for the treatment of perioperative hypertension (4), but the study did not examine clinical outcomes associated with the treatments. The trend to favor highly selective drugs with very short pharmacokinetic half-lives for use in the perioperative setting where hemodynamic changes occur rapidly and often unpredictably led to the development of clevidipine (5-6). The ESCAPE (7-8) and ECLIPSE (9) trials were performed in the process of obtaining FDA approval for the use of clevidipine for the treatment of perioperative hypertension, but were also the first large multi-center, randomized clinical trials to directly compare the safety and efficacy of different agents for the treatment of perioperative hypertension together with short-term clinical outcomes. At around the same time, the results of other large clinical trials such as the POISE trial (10) examining the use of beta-blockers in the perioperative period and the IMAGINE trial (11) examining the routine administration of ACE-inhibitors in the early postoperative period have contributed important information to guide the use of antihypertensive drugs used to manage surgical patients during and shortly after operation.

ESCAPE-1 Trial: Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgical patients. Anesth Analg 2007;105:918-25
This study tested the efficacy of clevidipine in comparison to placebo for treating preoperative hypertension in 152 cardiac surgical patients. Clevidipine (0.4 – 8.0 mcg/kg/min) had a 92.5% success rate (versus 17.3% success rate for placebo, p = 0.0001) in decreasing systolic blood pressure by ≥15% at a median time of 6.0 minutes. There were no differences in the type or rates of adverse events in the treatment groups.


This study tested the efficacy of clevidipine in comparison to placebo for the treatment of acute postoperative hypertension (SBP ≥ 140 mm Hg) within 4 hours after cardiac surgery in 206 patients. Clevidipine (0.4 – 8.0 mcg/kg/min) had a 91.8% success rate (versus 20.4% success rate for placebo, p = 0.0001) in decreasing systolic blood pressure by ≥15% at a median time of 5.3 minutes. There were no differences in the type or rates of adverse events in the treatment groups.

The ECLIPSE Trials: Comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and Nicardipine for acute hypertension treatment in cardiac surgical patients. Anesth Analg 2008;107;1110-21

The ECLIPSE trials consisted of three prospective, randomized, open-labeled studies comparing clevidipine to nitroglycerin (n = 628), clevidipine to sodium nitroprusside (n = 739), and clevidipine to nicardipine (n = 597) for the treatment of perioperative hypertension in cardiac surgical patients. The incidence of myocardial infarction, stroke, or renal dysfunction was not different among the treatment groups, but mortality was significantly greater in the sodium nitroprusside group compared to the clevidipine group (4.7% v. 1.7%, p = 0.04). The effectiveness of treatment measured by the extent and duration of excursions of the systolic blood pressure beyond predetermined limits demonstrated that clevidipine was more effective than nitroglycerin (p = 0.0006), more effective than sodium nitroprusside (p = 0.003), and equivalent in effectiveness to nicardipine. The study demonstrated that clevidipine provided more precise control of systolic blood pressure when used to treat perioperative hypertension in comparison to nitroglycerin and sodium nitroprusside. The increased mortality observed in the sodium nitroprusside treatment group was not attributed to any specific cause, but did raise concern for the recognized safety issues associated with this drug.


This study tested the effect of beta-blocker therapy with extended-release metoprolol succinate (target dose 200 mg/day) in a randomized, placebo-controlled trial involving 8,351 patients with or at risk for atherosclerotic disease undergoing non-cardiac operations. Fewer patients in the metoprolol group suffered non-fatal myocardial infarction (3.6% v. 5.1%, p = 0.0008) or required myocardial revascularization (0.3% v. 0.6%, p = 0.0123), but had greater overall mortality (3.1% v. 2.3%, p = 0.0317) and a higher incidence of stroke (1.0% v. 0.5%, p = 0.0053). The results of this study was
interpreted by the authors to support the effectiveness of perioperative beta-blocker therapy to reduce the risk of myocardial infarction, myocardial ischemic events, and clinically significant atrial fibrillation, but at the expense of an increased the risk of stroke and death. Post-hoc analysis suggested that clinically significant hypotension, bradycardia, stroke, and sepsis in the metoprolol-treated group may have been factors explaining the greater mortality in that group.


This study tested if ACE-inhibitor therapy initiated early after CABG would reduce the incidence of coronary ischemic events, stroke, or congestive heart failure in patients with preserved left ventricular function. In the trial, 2,553 patients undergoing CABG were randomized to quinapril (target dose of 40 mg/day) or placebo. The incidence of the composite end-point for adverse events was significantly greater in the quinapril group within in the first 3 months after CABG (hazard ratio = 1.52, p = 0.0356). The study concluded that although evidence supports the usefulness of ACE-inhibitors in patients with coronary artery disease, early (<7 days) postoperative initiation of ACE-inhibition in patients without a clear indication for the therapy was not beneficial and may even increase the incidence of adverse events in low risk patients. In patients with an indication for ACE-inhibitor therapy early after CABG, treatment should be administered with care and in very small doses.

**References:**


