クロニジンは相殺による有益性はもたらさずリスクを上昇させる

POISE-2：クロニジンは非心臓手術後の死亡や心筋梗塞を減少させない

POISE-2: Clonidine does not reduce deaths or myocardial infarction after non-cardiac surgery

クロニジンは非心臓手術後の臨床的に問題のある血圧低下や非致死性心停止発現率を上昇させるとのPOISE-2トライアルの結果が第63回American College of Cardiology学会で発表され、*New England Journal of Medicine*オンライン版に掲載された。心血管系リスクを有する収縮期血圧105mmHg以上および心拍数55bpm以上の患者が入院手術前にクロニジンまたはプラセボ群にランダムに割り付けられた。クロニジン群（5,009人）は0.2mgのクロニジン錠を術前に、同用量となる貼付剤を術後72時間にわたり投与された。プラセボ群（5,001人）は対応する錠剤および貼付剤を与えられた。その結果、ランダム化後30日間の死亡率および非致死性心筋梗塞（MI）からなる一次エンドポイントはクロニジン群で365件およびプラセボ群で339件であり、クロニジンはこれを改善させなかった。クロニジン群でMI数増加が認められた（クロニジン群325件対プラセボ293件）が統計学的に有意ではなかった。しかし、2つの二次エンドポイントは有意であった：臨床的に重要な血圧低下はクロニジン群患者の2,385人（48%）に認められたのに対しプラセボ群では1,854人（37%）であり、非致死性心停止はクロニジン群で16件であったのに対しプラセボ群では5件であった。

Full Text

Clonidine – a drug that reduces blood pressure and heart rate – increased rates of clinically concerning hypotension and non-fatal cardiac arrest after noncardiac surgery, according to the POISE-2 trial presented at the American College of Cardiology's 63rd Annual Scientific Session and published online in the *New England Journal of Medicine*. With more than 10,000 patients in 23 countries, this randomized clinical trial is the largest study of clonidine in surgical patients.

The study's findings caught researchers by surprise. The earlier POISE-1 study found that beta-blockers greatly reduced risk of myocardial infarction (MI) during and after non-cardiac surgery, but increased risk of devastating strokes and mortality. In POISE-2, researchers used low-dose clonidine, which smaller studies had suggested would provide the heart-protecting benefits of beta-blockers without increasing stroke risk. (POISE-2 also examined aspirin in this setting. Those results are presented separately at ACC.14.)

Patients at cardiovascular risk with a systolic blood pressure of at least 105 mm Hg and a heart rate of at least 55 beats per minute were randomly assigned to clonidine or placebo before inpatient surgery. The clonidine group (5,009 patients) was given 0.2 mg clonidine in tablet form before surgery and a skin patch that delivered the same dose daily for 72 hours after surgery. The placebo group (5,001 patients) was given matching tablets and patches.

Clonidine failed to improve the primary outcome of mortality and non-fatal MI at 30 days after randomization, with 365 events for clonidine and 339 for placebo. The clonidine group had a non-significant increase in the number of MIs (325 clonidine vs. 293 placebo), but two secondary measures were significant: clinically important hypotension was seen in 2,385 clonidine patients (48 percent) versus 1,854 placebo patients (37 percent), and 16 clonidine patients had non-fatal cardiac arrest versus five in the placebo group. Patients will be followed for one year.

"Clonidine should not be given to patients having non-cardiac surgery in an attempt to reduce perioperative mortality or MI," said Daniel I. Sessler, M.D., Michael Cudahy professor and chair of the Outcomes Research Department at the Cleveland Clinic and a study investigator. "If anything, it worsens the outcome, probably by reducing blood pressure." He speculated that clonidine didn't perform as expected because it caused hypotension out of proportion to its protective effect on heart rate.

All available information suggested that the POISE-2 drug, clonidine, would improve outcomes. "That it did not prove effective tells us that the perioperative setting presents unique challenges and will require special approaches," Sessler said.

An obvious next target for study is a drug that controls heart rate without lowering blood pressure, such as ivabradine, an If-channel blocker used to treat stable angina, he said.

The study was funded by the Canadian Institutes of Health Research. None of the investigators has a personal financial interest in the research.

ACC2014特集