

Critically Appraised Topic

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Should patients at lower cardiac risk receive beta-blockers before noncardiac surgery?

A 74-year-old female is admitted to the orthopedic service after a fall, which resulted in a left femoral-neck hip fracture requiring surgical repair. The hospital internal medicine service is consulted for a preoperative medical examination. Her medical history is significant for hypertension, hyperlipidemia, type 2 diabetes mellitus, and an ischemic stroke 2 years ago. She has no history of coronary artery disease or heart failure and denies any history of exertional angina, dyspnea, palpitations, dizziness, or recent syncope. At the time of the examination, the patient's only complaint is left hip pain. Vital signs are within normal limits. Cardiac, pulmonary, and abdominal examinations are unremarkable. Her left leg is shortened and externally rotated but neurovascularly intact. Results of laboratory studies are unremarkable. Chest radiography and electrocardiography are normal. The patient's medication list includes hydrochlorothiazide, 25 mg daily; simvastatin, 20 mg at night; metformin, 500 mg twice a day; and aspirin, 81 mg daily.

According to the Revised Cardiac Risk Index,^{1,2} the patient is at intermediate risk, scoring 1 point for her past stroke. Although the patient has cardiac risk factors, noninvasive cardiac testing is not required before proceeding to the operating room. However, you question whether she may benefit from use of perioperative beta-blockers.

CLINICAL QUESTION

Does initiation of beta-blockers prior to noncardiac surgery reduce the risk of postoperative cardiovascular events

for patients who have cardiac risk factors but are not already on chronic beta-blocker therapy?

SEARCH CRITERIA AND RESULTS

This question falls under the general category of *therapy*. The highest levels of evidence to help answer questions about therapy are high-quality meta-analyses; systematic reviews; or very large, well-conducted, randomized controlled trials (RCTs).

We conducted a search of the medical literature using the following terms in MEDLINE 1966-current: *adrenergic beta-antagonists AND perioperative care*. Adrenergic beta-antagonists yielded 32,576 results, and perioperative care (exploded) yielded 65,018 results. Combining the terms yielded 293 articles. Limiting these to humans and English language reduced it to 238; that result was then limited to meta-analysis or RCT, resulting in 32. The abstracts of the excluded non-English papers were reviewed to ensure we did not miss a relevant study. Further searches of PubMed, evidence-based medicine prefiltered databases, the Cochrane databases, and online search engines failed to yield any additional articles that were more pertinent or of a higher level of evidence. Ultimately, the recently published Perioperative Ischemic Evaluation Study (POISE) trial³ was deemed to be the most pertinent trial addressing this clinical question.

EVALUATING THE EVIDENCE

The topic of perioperative use of beta-blockers serves as an excellent

example of how evidence-based medicine and clinicians' understanding and interpretation of research findings have influenced medical practice. In the late 1990s, two seminal trials generated a great deal of excitement in the field of perioperative medicine. Studies by Mangano and colleagues⁴ and Poldermans and colleagues⁵ both suggested that perioperative use of beta-blockers offered cardioprotective benefits for high-risk patients. So impressive were these results that the medical community began to enthusiastically implement the use of beta-blockers beyond the high-risk populations studied, namely, patients at low to moderate cardiovascular risk and those undergoing nonvascular surgery.⁶

Many of the initial trials purporting the benefit and "no harm" of perioperative beta-blockade were high-bias risk trials, small and insufficiently powered to address the effects on cardiovascular outcomes, used surrogate end points, had questionable study design, and potential for bias. For instance, the Mangano trial⁴ has been criticized because of significant discrepancies between the two study groups and the exclusion of deaths in the immediate postoperative period, which, if included at end-point analyses, would have negated the outcome of the study.⁷ Compelling evidence suggests trials like the Poldermans trial, which was stopped early for ben-

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efit, may systematically overestimate treatment effects.⁸ In fact, a number of trials published over the past decade have showed a lack of benefit in the perioperative application of beta-blockade, and raised concern about the harm, namely, bradycardia and hypotension.⁹⁻¹²

The POISE trial was designed to more directly test the utility of perioperative beta-blockade in low to moderate risk patients undergoing noncardiac surgery. It posed the question: Do patients with or at risk of atherosclerotic disease undergoing noncardiac surgery who receive perioperative extended-release metoprolol succinate versus placebo have fewer postoperative cardiac events?³ The POISE trial was an international, multicenter RCT conducted in 190 hospitals in 23 countries.

In the trial, 8,351 patients were randomized to receive either extended-release metoprolol succinate, a long-acting beta-blocker (n=4,174), or placebo (n=4,177). Treatment was initiated 2 to 4 hours before surgery and continued for 30 days. All patients, health care providers, data collectors, and outcome adjudicators were masked to treatment allocation. The primary end point was a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest. Analyses were by intention to treat. All 8,351 patients were included in the analyses; 8,331 (99.8%) completed the 30-day follow-up.³

The primary end point was lower in the metoprolol group compared with placebo, driven by a reduction in nonfatal MIs. However, an increased incidence of total mortality and stroke was seen. Stroke was associated with perioperative hypotension, bleeding, atrial fibrillation, and a history of stroke or transient ischemic attacks in patients assigned to receive metoprolol.

A starting dose of metoprolol succinate, 100 mg orally, was given 2 to 4 hours before surgery. Another 100-mg dose was administered 0 to 6 hours after surgery. Medication was held if the patient's systolic BP dipped below

100 mm Hg or if the heart rate was below 50 beats per minute. The protocol resulted in some patients receiving up to 200 mg of metoprolol. The POISE trial can be criticized for its use of a high dose of the beta-blocker, which undoubtedly contributed to the increased rates of hypotension, bradycardia, and ischemic stroke. However, this dose is supported by a large meta-analysis¹³ that confirms that tight heart rate control, avoiding hypotension, is associated with improved cardiovascular outcomes.

The POISE trial echoes cumulative data in the medical literature, suggesting that although long-acting beta-blockers appear to reduce perioperative cardiac events, they *increase* the incidence of stroke. The POISE trial clearly shows that acute administration of higher-dose beta-blocker therapy in the perioperative period is associated with greater risk than benefit. According to the POISE data, for every 1,000 patients with a similar risk profile undergoing noncardiac surgery, metoprolol will prevent MI in 15 patients and new significant atrial fibrillation in seven patients; however, it will cause death in eight patients and disabling stroke in five.

A subsequent meta-analysis of 33 randomized trials evaluated outcomes in 12,306 patients undergoing noncardiac surgery (of which more than 8,000 were from the POISE trial), utilizing a wide variety of beta-blockers and dosages.¹⁴ The authors estimated that treatment of 1,000 patients with beta-blockers resulted in 16 fewer nonfatal MIs in survivors but at the expense of 59 cases of hypotension, 45 cases of clinically significant perioperative bradycardia, three disabling strokes, and potentially increased mortality.¹⁴ However, both the POISE trial and the sensitivity analysis of the subsequent meta-analysis suggest that perioperative beta-blockers were associated with a lower risk of all-cause mortality and nonfatal MI in the high-surgical-risk subgroup.

CLINICAL BOTTOM LINE

Recent evidence suggests that patients at low to moderate cardiac risk who are undergoing noncardiac surgery do not benefit from perioperative initiation of beta-blockers. However, patients on chronic beta-blocker therapy should continue that therapy throughout the perioperative period. **JAAPA**

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