Perioperative beta blockade in noncardiac surgery: A review of the literature

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Perioperative beta blockade has been proven to significantly reduce the incidence of myocardial ischemia and myocardial infarction and of long-term overall mortality related to cardiac events after various surgeries in patients at intermediate or high risk for such events. The major physiologic effects of beta blockers result in a positive balance of myocardial oxygen supply and demand. Although the optimal timeframe for initiation of treatment is not clear from the available data, it has been shown that beta blocker therapy is effective when started at least 1 week before the scheduled surgery and continued throughout the postoperative period.

The current recommendations for perioperative beta blockade for patients at intermediate and high risk for a perioperative cardiac event are to use a β_1 blocking agent, begin therapy several weeks before a planned operation, titrate the dose to achieve a heart rate of 60 to 70 beats per minute, and taper the dose of the beta blocker after the postoperative period.

Key words: **Beta blockade, beta blockers, perioperative.**

There are approximately 25 million noncardiac operations performed annually in the United States. Of these 25 million operations, 3 million are performed on patients at risk for coronary artery disease, and 50,000 patients have a perioperative myocardial infarction (MI), of which 20,000 are fatal.[1]

The most significant risk factors for mortality and cardiovascular morbidity are myocardial ischemia and nonfatal MI during the first week after surgery.[2] One study found that postoperative ischemia increased the odds of postoperative myocardial events 21-fold.[3]

Myocardial ischemia occurs as a result of increased myocardial oxygen demand, reduced myocardial oxygen supply, or a combination of both. In the presence of coronary obstruction, an increase of myocardial oxygen requirements caused by tachycardia or stress leads to a transitory imbalance in myocardial oxygen supply and demand. This condition is frequently termed *demand ischemia*. In other situations, the imbalance is caused by an acute reduction of oxygen supply secondary to increased coronary vascular tone or as a result of platelet aggregates or thrombi. This condition is termed *supply ischemia*. In many circumstances, ischemia results from an increase in oxygen demand and a reduction in myocardial supply of oxygen.[4]

Beta blockers seem to have a substantial role in the prevention of perioperative cardiac complications. The major direct effects of beta blockers are reductions in heart rate (increasing diastolic perfusion time) and contractility (reducing oxygen demand).[5] Beta blockers also may indirectly influence the determinants of shear stress and reduce inflammation through decreases in sympathetic tone. Reductions in heart rate and pulse pressure and, therefore, mechanical stress, by beta blockers also are considered important in stabilizing vulnerable coronary plaques.[6,7] Surgery causes catecholamine surges and a prothrombotic state, which can, in turn, produce disrupted atherosclerotic lesions. Such complicated lesions can lead to clinical events in the weeks or months following surgery. Blocking the perioperative catecholamine surge could interrupt this process and might also account for the beneficial effect of beta blockade.[8]

Randomized trials of beta blocker use perioperatively

Stone et al,[9] in a study of patients with untreated hypertension undergoing elective surgery, showed a reduction in myocardial ischemia from 28% of patients in the control group compared with 2% in patients receiving a beta blocker. The authors did not report the types of procedures included in their sample, nor did they statistically compare baseline patient characteristics, leaving their conclusions open to debate. Raby et al[10] also found a significant reduction in postoperative myocardial ischemia in high-risk patients undergoing vascular surgery who received a continuous infusion of esmolol postoperatively. Urban et al[11] also found a reduction in perioperative

myocardial ischemia in patients treated with beta blockers in the immediate postoperative period, but their results did not reach statistical significance.

Of the studies reporting cardiac events and cardiac mortality in patients undergoing noncardiac surgery, 2 (Mangano et al[8] and Poldermans et al[12]) reported significant improvement in patient outcomes due to beta blockade.

Mangano et al[8] performed a randomized, double-blind study to compare the effect of atenolol with that of a placebo on overall survival and cardiovascular morbidity in patients who were undergoing noncardiac surgery with coronary artery disease (history of MI; typical angina; or atypical angina with a positive stress test result) or were considered at risk for coronary artery disease (2 or more of the following: older than 65 years, hypertension, currently smoking, cholesterol level >240 mg/dL, or diabetes). The study population included 200 men. Of the 200 patients enrolled in this study, 99 were randomized to receive atenolol, 5 to 10 mg, intravenously 30 minutes before surgery, and 101 patients received a placebo. Beginning on the morning after surgery, patients in the atenolol group received 10 mg of atenolol intravenously or 50 to 100 mg/d by mouth throughout the hospital stay for up to 7 days, and patients in the control group similarly received a placebo. All patients in the study underwent general anesthesia with endotracheal intubation. All of the patient's prescription medications were continued until the time of surgery, with beta blockers replaced by the study drug on the morning of surgery.

Of the 200 patients, 194 survived to be discharged from the hospital, and 192 were followed up for a period of 2 years (1 was lost to follow-up, and 1 was not followed up because surgery was not performed after the study drug was administered). Six patients died during hospitalization; 3 of the deaths were related to MI (2 patients in the placebo group and 1 in the atenolol group). During the 2-year follow-up period, 30 patients died. Of these deaths, 21 (12 of which were of cardiac causes) occurred in the placebo group, and 9 (4 of which were of cardiac causes) in the atenolol group; thus, overall mortality was 55% lower in the atenolol group, and the mortality from cardiac causes was 65% lower. The principal effect of atenolol therapy was on cardiac outcomes occurring during the first 6 to 8 months (1 death of noncardiac causes in the atenolol group vs 10 in the placebo group, 7 of which were of cardiac causes). After 8 months, there was no substantial difference between the groups; however, the early survival advantage in the atenolol group remained stable at the 1-year mark (97% vs 86%) and the 2-year mark (90% vs 79%).

Atenolol-treated patients who survived to hospital discharge had a significantly lower rate of cardiac events compared with the rate in the placebo group. Within 6 months after surgery, there were no events in the atenolol group compared with 12 in the placebo group, a decrease of 67% from the rate in the placebo group within 1 year and a decrease of 48% in the 2 years after surgery.

The results of this study showed favorable long-term benefits of perioperative beta blockade, and Wallace et al,[13] in a subset analysis of data from this study, reported reduced perioperative myocardial ischemia in the atenolol-treated patients. However, atenolol did not significantly reduce the incidence of death of cardiac causes during hospitalization or that of perioperative MI. The failure of atenolol to reduce the number of perioperative MIs may be reflective of the low incidence of serious cardiac events in the study population.

Although the results of this study are generally well accepted, it has many limitations. The study included patients with known coronary artery disease and those with only coronary risk factors, and the patients underwent a wide variety of surgical procedures. There were slightly higher frequencies in the placebo group than in the atenolol group of patients older than 65 years (65 in the atenolol group vs 75 in the placebo group), previous MI (18 atenolol vs 26 placebo), angina pectoris (25 atenolol vs 36 placebo), and diabetes (28 atenolol vs 35 placebo). However, adjustment for these differences in multivariate models did not alter these findings. The sample included only men and was conducted at only 1 hospital, which may limit the generalizability of the results. Also, patients who were randomized into the placebo group and were previously taking beta blockers before the surgery experienced abrupt withdrawal of the beta blocker for the intraoperative and postoperative period (up to 7 days).

Three years after this study by Mangano et al,[8] Poldermans et al,[12] reported a study showing a reduction in the perioperative incidence of death of cardiac causes and nonfatal MI in patients receiving perioperative beta blockade with bisoprolol. Poldermans et al[12] conducted a randomized, nonblinded, placebo-controlled study of a specific high-risk group of patients who showed evidence of cardiac disease by clinical predictors of cardiac risk and dobutamine stress echocardiography (DSE). Between 1996 and 1999, Poldermans et al[12] screened all patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction at 7 participating centers. All patients with 1 or more cardiac risk factors (N = 846) underwent DSE. Of these 846 patients, 173 had posi-

tive results on the DSE and were considered at high risk for perioperative cardiac complications. Patients were excluded if they were already taking a beta blocker or if they showed extensive wall-motion abnormalities during stress testing.

Eligible patients were assigned randomly to receive standard perioperative care or standard care plus bisoprolol. Treatment with bisoprolol was started at least 1 week before surgery and continued for 30 days postoperatively. The initial dose of bisoprolol was 5 mg orally once a day. After 1 week, patients were reassessed, and the dose was increased to a maximum of 10 mg once daily if the heart rate remained more than 60 beats per minute. The same dose was continued through the postoperative period. Patients were monitored for cardiac events during the 30-day postoperative period by 12-lead electrocardiogram (ECG) and serial serum creatinine kinase levels on postoperative days 1, 3, and 7.

Of the 173 patients who had positive DSE results, 61 were excluded from randomization because they were already taking beta blockers (n = 53) or showed extensive wall-motion abnormalities (n = 8). The remaining 112 patients underwent randomization, with 59 assigned to receive bisoprolol and 53 to receive standard care alone.

There were no significant differences between groups in clinical characteristics, results of DSE, surgical procedures, anesthetic technique, or intensive care unit course.

Nine patients in the standard care group (17%) died of cardiac causes during the postoperative period, compared with 2 patients (3%) in the bisoprolol group. Nine patients in the standard care group had a nonfatal MI, compared with none in the bisoprolol group. The overall rate of the combined end point of death of cardiac causes or nonfatal MI was 34% in the standard care group, compared with 3% in the bisoprolol group. The significant difference between groups in the incidence of serious cardiac events prompted the safety committee to interrupt the study after the planned interim analysis.

The limitations of this study include that it was not conducted in a blinded manner, it studied only a specific high-risk group of patients, and screening for a MI with cardiac enzyme levels and ECG recording was performed only during the first week after surgery. After the first 7 postoperative days, testing for an MI with cardiac enzyme levels or a 12-lead ECG was at the discretion of the anesthesiologist, who was not blinded to the study groups. However, postoperative MI is most common 48 to 72 hours after surgery and would have been detected by the routine testing during the first postoperative week.

Who should receive perioperative beta blockers?

Major predictors of increased perioperative cardiovascular risk are a recent unstable coronary syndrome such as an acute MI (documented MI <7 days previously), recent MI (>7 days but <1 month before surgery), unstable or severe angina, evidence of a large ischemic burden by clinical symptoms or noninvasive testing, decompensated heart failure, significant arrhythmias (high-grade atrioventricular block, symptomatic arrhythmias in the presence of underlying heart disease, or supraventricular arrhythmias with uncontrolled ventricular rate), and severe valvular disease.[14-16]

Intermediate predictors of increased risk are mild angina pectoris, a more remote previous MI (>1 month before planned surgery), compensated heart failure, preoperative creatinine level of 2.0 mg/dL or more, and diabetes mellitus.[14-16]

Minor predictors of risk are advanced age, abnormal ECG rhythm other than sinus, low functional capacity, history of stroke, serum cholesterol concentration at least 240 mg/dL, and uncontrolled systemic hypertension.[14-17] Auerbach and Goldman[17] suggest perioperative use of beta blockers in patients meeting any of the intermediate- or high-risk criteria or at least 2 of the low-risk criteria.

Surgery-specific risk of a myocardial event for noncardiac surgery is related to 2 important factors: the type of surgery being performed and the degree of hemodynamic stress associated with the procedure.

Surgery-specific risk for noncardiac surgery can be stratified as high (reported cardiac risk often >5%), intermediate (reported cardiac risk generally <5%), and low (reported cardiac risk generally <1%).[14,18,19] High-risk surgery includes major emergency surgery, particularly in elderly people; aortic and other major vascular surgery; peripheral vascular surgery; and anticipated prolonged procedures associated with large fluid shifts and/or blood loss. Intermediate-risk procedures include intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, and prostate surgery. Low-risk procedures include endoscopic and superficial procedures, cataract surgery, and breast surgery. Low risk procedures in patients with 0 or 1 cardiac risk factors generally do not require further testing or perioperative beta blockade.[20]

Agents and goals of therapy

Studies to date showing benefit of beta blockade on perioperative mortality and myocardial ischemia have used β_1 selective agents, as opposed to nonselective beta blockers.[8-11,14] There is no evidence that suggests

an advantage of one β_1 selective blocking agent over another. Randomized controlled trials of the effectiveness of perioperative beta blockade have used target heart rate as the indicator for therapeutic beta blockade.[8,10,11,14] Reduction of the resting heart rate to less than 70 beats per minute is a commonly used parameter. Poldermans et al[12] suggest that the goal should be to reduce the heart rate to less than 70 beats per minute preoperatively and to less than 80 beats per minute in the immediate postoperative period.

When to start beta blocker therapy

The American College of Cardiology–American Heart Association perioperative guidelines recommend that patients with inducible ischemia receive beta blockade, titrated to a resting heart rate of 50 to 60 beats per minute, starting days to weeks before a planned surgical procedure.[21] The optimal timeframe for initiation of treatment is not clear from the available data. Mangano et al[8] used intravenous atenolol in the immediate preoperative and operative periods to achieve a therapeutic dose, whereas Poldermans et al[12] initiated treatment an average of 1 month before surgery, using an oral agent. Both studies showed positive outcomes. Although it has been speculated that longer-term therapy may allow for the benefit of cellular-level effects,[22] there is no evidence that safety or efficacy is affected by immediate perioperative initiation of therapy.

When to stop beta blocker therapy

Abrupt discontinuation of beta blocker therapy can be hazardous. Hyperadrenergic withdrawal responses can be minimized by tapering before discontinuing the drug. Shammash et al[23] observed that immediate postoperative discontinuation of beta blockade for patients who had not received previous long-term therapy placed them at an increased risk for postoperative MI. This phenomenon was not observed in studies using shorter durations of treatment.[9,10] Auerbach and Goldman[17] recommend that therapy be continued at least through hospitalization, and longer if possible. This type of follow up allows for adequate tapering, if the patient is to discontinue treatment, or for proper continuity of therapy, if the patient is to maintain long-term beta blockade. According to London et al, [6] it is reasonable for therapy in low- to moderate-risk patients to be continued for the first week postoperatively, whereas patients undergoing vascular surgery, with its higher event rate, should continue therapy for 14 to 30 days postoperatively.

Contraindications to perioperative beta blockade

Many patients for whom this therapy traditionally was withheld tolerate careful titration of β_1 selective agents. A meta-analysis by Salpeter et al[24] suggests that cardioselective beta blockers are well tolerated in patients with reactive airway disease, asthma, and chronic obstructive pulmonary disease. Khosla et al[25] conducted a study to evaluate the safety of therapeutic beta blockade in patients with coexisting bronchospastic airway disease and coronary artery disease. The study included 30 patients with bronchospastic disease and active use of inhaled bronchodilators. One patient had recurrent bronchospasm that was lifestyle limiting while receiving 100 mg of atenolol daily, and 3 patients (10%) reported increased need for inhaled β_2-receptor agonist drugs for symptoms. No patients required hospital admission related to beta blocker induced bronchospasm.

Other contraindications to beta blocker therapy that have been examined and disproved include impaired left ventricular function, peripheral vascular disease, depression, and advanced age.[24] Although β_1 selective agents exhibit a lower potential for side effects at routine clinical doses, the potential increases with increasing doses.[6,25] Absolute contraindications to the use of beta blockers are major atrioventricular nodal conduction disease in the absence of a pacemaker, severe asthma, strong reactive airway disease, and previously documented sensitivities. Acute perioperative beta blockade should be avoided in the case of acute sepsis or hypovolemia.

Summary

Perioperative beta blockade has been proven to significantly reduce the incidence of myocardial ischemia, MI, and long-term overall mortality related to cardiac events after various surgeries in patients at intermediate or high risk for such events.

Despite strong evidence that perioperative beta blockade is efficacious in reducing perioperative morbidity and mortality, surveys of anesthesiologists show that these clinicians are still choosing not to exploit this therapy. According to a recent study by Schmidt et al, of the 67 patients determined to be candidates for beta blocker therapy of 158 patients undergoing noncardiac surgery, only 25 (37%) received perioperative beta blocker therapy.[26] Similarly, a recent survey of Canadian anesthesiologists found that although 93% of anesthesiologists surveyed agreed that beta blockers were beneficial in patients with known coronary artery disease, only 57% reported always or usually administering prophylactic beta blockers in these patients, and only 34% of these regular users continued therapy beyond the early postoperative period. Only 9% of respondents reported that a formal protocol existed at their facility.[27] VanDenKerkhof et al[27]

suggest that controversies in the literature and practical considerations may be barriers to implementation of perioperative beta blockade rather than lack of awareness of the current best evidence.

There is a large gap between the knowledge of anesthesia care providers regarding the benefits of perioperative beta blockade and actual administration of beta blockers for the appropriate populations. Perhaps this gap will be narrowed as more definitive information is obtained from larger studies in this area. One such ongoing study is the Perioperative Ischemic Evaluation Study (POISE Trial).[28] The POISE Trial is a large, Canadian, multicenter, randomized controlled trial of metoprolol vs placebo in 10,000 at risk patients undergoing noncardiac surgery. The study began in October 2002 and is expected to conclude in 2007.[28]

Although there is a need for a larger study to really understand the beneficial effects of perioperative beta blockade, enough evidence exists to provide guidelines for implementation of a protocol for perioperative beta blockade. The current recommendations for perioperative beta blockade for patients at intermediate and high risk for a perioperative cardiac event are to use a β_1 blocking agent, begin therapy several weeks before a planned operation, titrate the dose to achieve a heart rate of 60 to 70 beats per minute, and taper the dose of the beta blocker after the postoperative period.

REFERENCES

1. Belzberg H, Rivkind A. Preoperative cardiac preparation. *Chest.* 1999;115(5 suppl):82S-95S.
2. Mangano D, Goldman L. Current concepts: preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med.* 1995;333:1750-1756.
3. Landesberg G, Luria MH, Covet S, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular study. *Lancet.* 1993;341:715-719.
4. Zevitz ME. Myocardial Ischemia. *EMedicine.* Available at: www.emedicine.com/med/topic1568.htm. Accessed April 17, 2004.
5. Kertai MD, Bax JJ, Klein J, Poldermans D. Is there any reason to withhold beta-blockers from high-risk patients with coronary artery disease during surgery? *Anesthesiology*. 2004;100:4-7.
6. London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative β-adrenergic receptor blockade. *Anesthesiology.* 2004;100:170-175.
7. Jakobsen CJ, Bilee S, Ahlburg P, et al. Preoperative metoprolol improves cardiovascular stability and reduces oxygen consumption after thoracotomy. *Acta Anaesthesiol Scand.* 1997;41:1324-1330.
8. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: multicenter study of perioperative ischemia research group. *N Engl J Med.* 1996;335:1713-1720.
9. Stone JG, Foex P, Sear JW, et al. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. *Anesthesiology.* 1988;68:495-500.
10. Raby KE, Brull SJ, Timimi F, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. *Anesth Analg.* 1999;88:477-482.
11. Urban MK, Markowitz SM, Gordon MA, et al. Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. *Anesth Analg.* 2000;90:1257-1261.
12. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med.* 1999;341: 1789-1794.
13. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia: MsSPI Research Group. *Anesthesiology.* 1998;88:7-17.
14. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100:1043-1049.
15. Sear JW, Higham H. Issues in the perioperative management of the elderly patient with cardiovascular disease. *Drugs Aging.* 2002;19: 429-451.
16. Boersma E, Poldermans D, Bax J, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta blocker therapy. *JAMA.* 2001; 285:1865-1873.
17. Auerbach AD, Goldman L. β-Blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA.* 2002;287: 1435-1444.
18. Palda VA, Detsky AS. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. *Ann Intern Med.* 1997;127:309-312.
19. Ashton CM, Petersen NJ, Wray NP, et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med.* 1993;118:504-510.
20. Cina RA, Froehlich JB, Hamdan AD. Perioperative beta blockade to reduce cardiac morbidity in noncardiac surgery. *Int Anesthesiol Clin.* 2001;39:93-104.
21. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation.* 2002;105:1257-1267.
22. Zaugg M, Schaub MC, Pasch T, Spahn DR. Modulation of beta-adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action. *Br J Anaesth.* 2002;88:101-123.
23. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J.* 2001;141:148-153.
24. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med.* 2002;137:715-725.
25. Khosla S, Kunjummen B, Khaleel, et al. Safety of therapeutic β-blockade in patients with coexisting bronchospastic airway disease and coronary artery disease. *Am J Ther.* 2003;10:48-50.
26. Schmidt M, Lindenauer PK, Fitzgerald JL, Benjamin EM. Forecasting the impact of a clinical practice guideline for perioperative β-blockers to reduce cardiovascular morbidity and mortality. *Arch Intern Med.* 2002;162:63-69.
27. VanDenKerkhof EG, Milne B, Parlow JL. Knowledge and practice regarding prophylactic perioperative beta blockade in patients undergoing noncardiac surgery: a survey of Canadian anesthesiologists. *Anesth Analg.* 2003;96:1558-1565.
28. Devereaux PJ, Yang H. POISE Trial. Clinical Trials.gov. Available at: www.clinicaltrials.gov/ct/gui/show/NCT00182039. Accessed December 14, 2005.

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