Chapter 25. Beta-blockers and Reduction of Perioperative Cardiac Events

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Background

As the most common complications of major noncardiac surgery, myocardial infarction and cardiovascular death have long been a focus of preoperative evaluations[1-4] and a target of perioperative management strategies. Until recently, methods to reduce the incidence of these complications depended upon preoperative assessments of risk combining clinical evaluation with clinical prediction rules, followed by additional tests or revascularization procedures, as appropriate.[1] The benefit of preoperative revascularization remains unclear, as no randomized prospective trial has demonstrated its benefit.[5] Indeed, concern exists that preoperative intervention might prove detrimental, as the net benefit in terms of reduced perioperative cardiac events may be offset by the risks of the revascularization strategy itself. Newer strategies, including the use of percutaneous transluminal angioplasty as the revascularization modality, may have promise.[6] Large prospective trials examining these approaches are underway.[5]

Strong evidence links myocardial ischemia with postoperative myocardial events.[7,8] One study found postoperative ischemia increased the odds of postoperative myocardial events 21-fold.[9] Based on findings from observational studies that beta-blockade blunts electrocardiographic signs of ischemia,[10-12] recent trials have examined the effects of perioperative beta-blocker administration on patient outcomes. Results of these investigations are extremely promising, and beta-blockade may represent an important new method of reducing perioperative cardiac risk. This chapter reviews the evidence from randomized controlled trials examining the effect of perioperative beta-blockade on cardiac events (ie, myocardial ischemia, angina, myocardial infarction, pulmonary edema, and cardiac death).

Practice Description

Although published studies have employed different agents, doses, and dosing schedules, the general approach in each study has been similar: administration of a therapeutic dose of beta-blocker prior to induction of anesthesia, followed by beta-blockade through the operation and in the postoperative period. In all regimens, the dose is titrated to a target heart rate, generally 70 beats per minute or lower.

Prevalence and Severity of the Target Safety Problem

Myocardial cardiac events are the most common medical complication of surgery, occurring in 2-5% of patients undergoing non-cardiac surgery[13] and as many as 30% of patients undergoing vascular surgery.[14,15] Perioperative cardiac events are associated with a mortality rate of nearly 60% per event,[14,16] prolonged hospitalization, and higher costs.[16,17] The prevalence of these events and their high mortality have made the prevention of perioperative cardiac ischemia the subject of practice guidelines[1,17] and numerous prediction rules[13,16,18] to detect patients at high risk for these complications.

Opportunities for Impact

As a relatively new therapy, few data describe the use of perioperative beta-blockade in clinical practice. However, evidence suggests it is utilized infrequently. A recent observational study in the Netherlands of patients undergoing vascular surgery showed that only 27% of these high-risk patients received beta-blockers perioperatively.[19]

Study Designs

Using a structured MEDLINE search, we identified 4 relevant randomized controlled trials of the effectiveness of perioperative beta-blockade in reducing perioperative cardiac events, including myocardial ischemia and cardiac or all-cause mortality (Table 25.1). A randomized trial by Harwood et al was excluded because both groups received beta-blockers (ie, there was no control group).[20] Although data from a study by Wallace et al[21] were derived from one of the randomized trials included in this review,[22] it reported effects of beta-blockade upon different outcomes (ie, myocardial ischemia) and was included in our review. There was sufficient evidence available to limit the review to studies of Level 1 design. Observational studies, such as those by Pasternack et al and Boersma et al,[11,19] are not included.

Study Outcomes

The studies identified included a range of clinical outcomes: 2 included assessment of myocardial ischemia[12,23] and 3 reported myocardial infarction, pulmonary edema, cardiac death, or all-cause mortality (Level 1 outcomes).[15,22,23]

Evidence for Effectiveness of the Practice

Of studies reporting the effect of beta-blockers on perioperative ischemia (Level 2 outcome), all but one found a statistically significant reduction in ischemia among treated patients. Wallace et al,[21] in a subset analysis of data from Mangano et al,[24] reported less frequent perioperative myocardial ischemia in atenolol-treated patients. Stone et al[25] suggested a similar effect of beta-blockade on Holter-monitor documented myocardial ischemia. However, 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[12] also found a significant beneficial effect of beta-blockade using a continuous infusion of esmolol in high-risk patients undergoing vascular surgery. Although Urban et al also found a reduction in perioperative ischemia, this difference failed to reach statistical significance.[23] These findings may be explained in part by a relatively low cardiac risk in Urban's cohort, who were undergoing elective total knee replacement. The patients in many of the other studies were at higher risk of cardiac events, as demonstrated by rates of ischemia in the control groups. In studies finding a statistical difference, rates of ischemia were between 28% and 73% in controls, as compared with the 15% rate of ischemia observed in Urban's control group.

Of studies reporting cardiac events and cardiac mortality, 2 reported significant improvement in patient outcomes due to beta-blockade. In a study of male veterans undergoing major noncardiac surgery, Mangano et al[22] reported a relative reduction in all-cause mortality of nearly 55% at 2 years. This difference, which appeared within the first 8 months of follow-up, was ascribed to a marked reduction in cardiac events in the first year of therapy (67% reduction at year 1, 48% at year 2). However, patients in the beta-blocker group had less coronary disease at study entry, were on ACE-inhibitors more frequently, and were less likely to have beta-blockers discontinued perioperatively, perhaps biasing results in favor of the treatment group.[26,

[27] Accounting for these differences in multivariate models of varying stringency did not invalidate their findings.[24] Although questions remain about the generalizability of results to other patient populations, the authors favored broader use of beta-blockade in the setting of clinical trials.

Poldermans et al[15] suggested an even greater benefit of beta-blockade among high-risk patients. These investigators enrolled patients undergoing vascular surgery who had myocardial ischemia documented by dobutamine echocardiography, with an estimated rate of perioperative cardiac event of 28%. The entire patient cohort experienced a 90% reduction in cardiac death or non-fatal myocardial infarction at 30 days. Follow-up care did not include additional therapy (ie, cardiac catheterization, revascularization), raising concerns that the research algorithm did not reflect optimal clinical practice.[28, 29] However, if the true rate of events in treated patients is low (the point estimate from this small study was 3.4%), the risks associated with revascularization[30] may outweigh any benefit.

In contrast to the previous 2 studies, Urban et al[23] found no statistically significant difference in rates of in-hospital myocardial infarction. It is likely that these investigators' ability to detect a difference was limited in part by the relatively small sample size and shorter length of follow-up. Other studies of perioperative beta-blockade employed longer periods of follow-up to detect events up to 2 years following surgery.

Differences in absolute magnitude of benefit can be ascribed in part to the cardiac risks of the patients enrolled (again reflected in event rates in the control groups in each study), with the most powerful benefits seen in patients at highest risk. The greater benefit seen in Poldermans et al's study[15] may also be due to the fact that the study did not enroll patients who were receiving beta-blockers. Patients who are beta-blocker naïve may have a different response to perioperative use of bisoprolol, or the preexisting use of these agents may represent a confounding factor not completely accounted for in other studies of perioperative beta-blockade.

Beta-blockade may have additional beneficial effects for elderly patients. Patients who received beta-blockers were extubated more quickly, required less medication for pain, and were alert sooner after surgery.[31] Although the unblinded nature of this study leaves its findings open to debate, the possibility of additional benefits is tantalizing and worthy of further investigation.

Potential for Harm

Stone et al reported high rates of bradycardia (21/89 patients) in beta-blocker treated patients, "half" of whom required atropine therapy. However, the vague descriptions and more general problems with the study's design make it difficult to interpret the significance of these events in clinical practice. Adverse events related to the use of beta-blockers in other reviewed studies were infrequent (10% or less in Mangano et al[22]) and did not require therapy or result in withdrawal of the medication. Similar rates of side effects have been noted in studies examining beta-blockade in patients undergoing cardiac surgery.[20,32,33] One study examining use of propranolol in patients undergoing thoracotomy for pneumonectomy suggested that patients receiving beta-blockers had twice the rate of postoperative congestive heart failure (4/50 vs. 8/50, $p<0.01$). In addition, 16% (8/50) of patients in the treatment arm had the drug discontinued due to "bronchospasm."[34]

Finally, a recent prospective observational study has suggested that withdrawal of beta-blockade from patients immediately following surgery may result in adverse events.[35] This effect was not observed in randomized trials of beta-blockade that employed shorter treatment regimens[12,25] and should be confirmed by larger studies.

Costs and Implementation

The costs of beta-blockers are generally low, and the systems required to use them according to the protocols used in these studies are already in place. In addition, there is the potential for significant cost-savings if routine use of beta-blockers allows a safe reduction in the use of extensive preoperative cardiovascular testing.

Comment

Results from several well-designed clinical trials suggest that use of beta-blockers in the perioperative period is associated with significant reductions in patient cardiac morbidity and mortality. In the future such therapy may reduce the need for additional tests and revascularization procedures,[14] further reducing costs of care. However, several questions regarding its use remain, and should be topics of future research.

First, no clear data suggest an advantage of one particular beta-blocking agent over another. Studies to date have employed several different beta-blockers, suggesting that the efficacy of beta-blockade is class dependent if titrated to physiologically active dosages. Other (alpha-1 selective) sympatholytics also improve patient outcomes,[36] raising the possibility that combined alpha-beta antagonists (ie, labetolol) may have benefit. Second, results from Shammash et al document the hazards of discontinuation of beta-blockers immediately postoperatively,[35] and most protocols employed treatment regimens that extended longer - even up to one month following surgery. The current studies suggest beta-blockade should be continued for at least one week postoperatively. Third, effectiveness of beta-blockade in patients at high risk due to aortic stenosis or unstable or severe cardiovascular symptoms (New York Heart Association Class III-IV) is unknown, as these patients were not included in the reviewed studies. Similarly, its utility - both in terms of cardiac events and cost - in patients with very low risk of perioperative cardiac events (ie, those undergoing same-day or outpatient surgery, ophthalmic surgery, or those who have minimal cardiac risk) is unclear. Beta-blockade has not been studied in patients undergoing regional anesthesia or conscious sedation. In addition, no study to date has examined the use of beta-blockade in patients who have poor functional status and might otherwise be referred for additional non-invasive testing.[1,5,14,17]

Finally, the increasing popularity of perioperative beta-blockade, particularly catalyzed by the results of the study by Poldermans et al,[15] calls into question whether risk stratification using published guidelines or risk indices is still necessary.[28] Although beta-blockade is likely to be effective in many patients, the identification of patients at highest risk is still important, as these patients may require additional testing and therapy. A recent study of beta-blockade noted improved outcomes across a spectrum of predicted cardiac risk, but noted that cardiac events could be further reduced in high-risk patients through use of additional non-invasive testing and subsequent "usual care."[19] Thus, although beta-blockade may increase the threshold at which clinicians refer patients for additional testing, the era of risk stratification is not over.

The use of beta-blockers to reduce perioperative cardiac events and mortality represents a major advance in perioperative medicine for some patients at intermediate and high risk for cardiac events during noncardiac surgery. Wider use of this therapy should be promoted and studied, with future research focused on fine-tuning dosages and schedules and identifying populations of patients in which its use is cost-effective.

Table 25.1. Randomized controlled trials of the effectiveness of perioperative beta-blockade*

Study	Participants	Regimen	Results†	Side Effects	Comments
Mangano, 1996[22] Wallace, 1998[21]	200 patients undergoing elective noncardiac surgery	Atenolol 5-10g IV 30 min before entry into OR, after surgery, and 50-100g qd through hospital stay (up to 7 days); Target HR 55-65 bpm; doses held if HR<55 bpm or SBP<100 mmHg or defined adverse event	All-cause mortality at 2 yrs: 9% vs. 21% (p=0.019) Cardiac death at 2 yrs: 4% vs. 12% (p=0.033) Postoperative ischemia: 24% vs. 39% (p=0.03)	Intraoperative bradycardia more common with atenolol (38% vs. 15%, p=0.0002) but no difference in need for treatment No increase in third-degree heart block, hypotension, bronchospasm, or congestive heart failure	Included patients already taking beta-blockers, an excess of which (18 vs. 8%) were in the beta-blocker group NNT 9.1 (primary endpoint)
Polderman s, 1999[15]	112 patients with positive results on dobutamine echocardiography undergoing elective abdominal aortic or infrainguinal arterial reconstruction	Bisoprolol 5-10 mg po qd, begun an average of 37 days preoperatively and continued for 30 days postoperatively. Doses held if HR<50 bpm or SBP<100 mmHg	Cardiac death: 3.4% vs. 17% (p=0.02) Nonfatal MI: 0% vs. 17% (p<0.001)	No exacerbations of peripheral vascular disease	Excluded patients already on beta-blockers NNT 3.2 (cardiac death or nonfatal MI)
Raby, 1999[12]	26 patients with preoperative ischemia by Holter monitor undergoing aortic aneurysm repair, infrainguinal arterial bypass, or carotid endarterectomy	Esmolol IV for 48 hr postoperatively. Titrate to HR 20% below ischemic threshold but no less than 60 bpm	Postoperative ischemia: 33% vs. 73% (p<0.05)	No patient had beta-blocker therapy suspended because of unacceptable side effects	Clinicians prescribed alternate postoperative beta-blockers more often in control group (13% vs. 82%, p<0.05) NNT 2.5 (primary endpoint)
Stone, 1988[37]	128 untreated hypertensive patients undergoing elective surgery. Hypertension	Patients randomized to control, labetolol 100 mg po, atenolol 50 mg po, or oxprenolol 20	Myocardial ischemia: 2/89 (2%) vs. 11/39 (28%) in untreated patients	21 patients with beta- blockers had bradycardia, "half required atropine." No bradycardia in	Patients had generally similar baseline characteristics, but these were not statistically

	defined as systolic blood pressure 160-200 mmHg, diastolic 90-100 mmHg	mg po given before induction of anesthesia	(p<0.001)	control patients	compared No description of surgeries performed
Urban, 2000[23]	120 patients undergoing elective total knee arthroplasty	Esmolol IV within 1 hr after surgery, titrate to HR<80 bpm. Change to metoprolol morning of 1st postoperative day. Titrate to HR<80 bpm for next 48 hrs then continue dose until discharge	Postoperative ischemia: 6% vs. 15% (p=NS) Postoperative MI 2% vs. 6% (p=NS)	None noted	Included patients already on beta-blockers (30% in each arm)

* HR indicates heart rate; MI, myocardial infarction; NNT, number needed to treat; and NS, not statistically significant.
† Results are reported as beta-blocker group vs. control group.

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