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Perioperative use of beta-blockers

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Abstract

Perioperative beta-blocker therapy has been considered a mainstay of perioperative cardioprotection in patients with or at risk of coronary artery diseases. However, current recommendations for perioperative beta blockade are based mainly on the findings of trials with inadequate methodology and data analysis. The recently published results of the first adequately powered large controlled randomized trial on the efficacy and safety of perioperative beta-blocker therapy confirmed the benefit of such therapy on the perioperative incidence of non-fatal myocardial infarctions. However, such a benefit occurred at the expense of increased total mortality and increased incidence of stroke, negating any beneficial effect. A subsequently published meta-analysis confirmed, in large part, these findings. Given these recent publications, most of the current recommendations for perioperative beta-blocker therapy are no longer supported by evidence, therefore respective revision is needed.

Introduction and context

Perioperative cardiovascular morbidity and mortality contribute greatly to overall perioperative morbidity and mortality. The perioperative period is frequently associated with a mismatch of myocardial oxygen supply and demand and may induce large, unpredictable, and unphysiological alterations in coronary plaque morphology, function, and progression. With many diverse factors involved, it is highly unlikely that a single intervention will successfully improve cardiac outcome following non-cardiac surgery. Based on the increasing knowledge of the nature of atherosclerotic coronary artery disease and of the benefits of aggressive cardiovascular medication in coronary artery disease in general, the paradigm is shifting from an emphasis on preoperative cardiac testing and coronary revascularization to aggressive pharmacological perioperative therapy. Perioperative beta-adrenoceptor antagonist (hereafter referred to as beta-blocker) therapy is one example of the latter. Numerous cardiovascular and other effects of beta-blockers may possibly contribute to perioperative cardioprotection [1].

Two randomized controlled trials seemed to support the effectiveness of perioperative beta blockade in improving cardiac outcome in patients with or at risk for coronary artery disease [2,3]. It had been suggested, mostly on the basis of these two studies, that beta-blockers should be administered to almost all patients with one or more cardiac risk factors [4]. However, both studies included just a little over 300 patients and had major flaws in study design and data analysis, which render the findings highly questionable. A meta-analysis performed in 2005 [5] and results of three subsequently published double-blind randomized placebo-controlled trials [6-8] failed to demonstrate a cardioprotective effect of perioperative beta-blocker therapy.

Recent advances

The POISE study

The investigation into perioperative beta-blocker therapy changed considerably after publication of the results of the POISE (PeriOperative ISchemic Evaluation) study [9]. This is the first adequately powered controlled randomized trial on the efficacy and safety of perioperative beta-blocker therapy. It was carried out in 190 hospitals in 23 countries. The goal of this trial was to compare the effectiveness of perioperative beta-blocker therapy with metoprolol with that of placebo on major

cardiovascular events during the first 30 postoperative days following non-cardiac surgery in patients with or at risk for atherosclerotic disease. Four thousand one hundred seventy-four patients were randomly assigned to the metoprolol group, and 4,177 to the placebo group. Underlying cardiovascular morbidity included coronary artery disease (43%), peripheral vascular disease (41%), and prior stroke (15%). Patients received metoprolol 100 mg controlled release (CR) or placebo 2-4 hours before surgery, and metoprolol 200 mg CR or placebo daily for 30 days postoperatively. The primary endpoints were combined cardiovascular death, non-fatal myocardial infarction, and cardiac arrest. Secondary endpoints were total mortality, cardiovascular mortality, need for coronary revascularization, atrial fibrillation, and clinically significant hypotension and bradycardia requiring therapy.

During the first 30 postoperative days, the primary endpoint was significantly less in the beta-blocker group compared with the placebo group (incidence 5.8% versus 6.9%, hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.70-0.99; $P = 0.04$). This was due primarily to a marked reduction in the incidence of non-fatal myocardial infarctions in the beta-blocker group (incidence 3.6% versus 5.1%, HR 0.70, 95% CI 0.57-0.86; $P = 0.0008$). The need for revascularization (0.3% versus 0.6%; $P = 0.01$) and the incidence of atrial fibrillation (2.2% versus 2.9%; $P = 0.04$) were also significantly lower in the group of patients that had received beta-blockers. However, in the beta-blocker group, total mortality (3.1% versus 2.3%, HR 1.33, 95% CI 1.03-1.74; $P = 0.03$) and the incidences of stroke (1.0% versus 0.5%, HR 2.17, 95% CI 1.26-3.74; $P = 0.005$), significant hypotension (15.0% versus 9.7%; $P < 0.0001$), and significant bradycardia (6.6% versus 2.4%; $P < 0.0001$) were higher, negating the beneficial effect of perioperative beta-blocker therapy on the primary endpoint. Incidences of intra- and postoperative clinically relevant hypotension were independent predictors of death and stroke. The higher incidence of hypotension in the metoprolol group might possibly explain the more frequent strokes.

As was to be expected, a multicenter study of this size will be prone to criticism on various grounds. Most criticism relates to (a) the dosage of metoprolol (considered by some to be too high), (b) the formulation (CR), (c) acute preoperative start of beta-blocker therapy without individual titration to effect, and (d) fixed dosages in the perioperative period during which cardiovascular physiology, pharmacokinetics, and pharmacodynamics may change within short periods of time. However, the dosage of metoprolol was compatible with recent recommendations [10]. The two studies on which the recommendations for perioperative beta-blocker therapy had largely been based had also used long-acting beta-blockers [2,3]. In addition, a large perioperative cohort study indicated that long-acting beta-blockers are more cardioprotective than short-acting ones [11]. Finally, dosage was adjusted (that is, medication was withheld if heart rate decreased to less than 45 beats per minute and systolic blood pressure to less than 100 mm Hg). Although the dosage in the POISE study was, indeed, eight times the equivalent of the dosage of bisoprolol used in the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) study [3], only 15% of patients treated with metoprolol in the POISE study developed hypotension. This is a lower incidence than reported in other studies [6]. A previous meta-analysis had shown that perioperative beta-blocker therapy is generally accompanied by an increased incidence of therapy-requiring hypotension (relative risk 1.27, 95% CI 1.04-1.56) [5]. The respective findings of the POISE study are comparable (relative risk 1.55, 95% CI 1.38-1.77). Finally, beta-blocker therapy had been started immediately prior to induction of anesthesia in one of the landmark studies [2]. Overall, the results of the POISE study can hardly be dismissed on the grounds of major flaws in study design [12, 13].

Meta-analysis by Bangalore et al.

A recently published meta-analysis (based on 33 randomized controlled trials that included a total of 12,036 patients) confirmed, in large part, the findings of the POISE study [14]. Perioperative beta-blocker therapy was associated with a 35% decreased risk for perioperative non-fatal myocardial infarction (odds ratio [OR] 0.65, 95% CI 0.54-0.79) (number needed to treat [NNT] = 63) at the expense of a doubling of the risk for non-fatal disabling strokes (OR 2.01, 95% CI 1.27-3.68) (number needed to harm [NNH] = 293) and for therapy-requiring hypotension (NNH = 17) and a tripling of the risk for therapy-requiring bradycardia (NNH = 22). Perioperative beta-blocker therapy was not associated with any significant risk reduction for all-cause mortality, cardiovascular mortality, or heart failure. This meta-analysis suggests that the perioperative treatment of 1,000 patients with beta-blockers can be expected to be associated with 16 fewer non-fatal myocardial infarctions in survivors at the expense of three non-fatal strokes, 45 patients with clinically relevant perioperative bradycardia, and 59 patients with clinically relevant perioperative hypotension and potentially increased mortality. This meta-analysis is methodologically sound and probably the most complete of all meta-analyses ever carried out in the area of perioperative beta-blocker therapy.

Relevance of heart rate control

The importance of strict heart rate control as a prerequisite for effectiveness of perioperative beta-blocker therapy has been emphasized repeatedly. A non-randomized non-blinded observational cohort study in 272 vascular surgery patients with documented coronary artery disease investigated the effect of different dosages of various beta-blockers and of tight perioperative heart rate control on the incidence of perioperative myocardial ischemia and myocardial cell injury [15]. High-dose perioperative beta-blocker therapy and tight perioperative heart rate control were associated with a reduced incidence of myocardial ischemic episodes, reduced release of cardiac troponin T, and improved long-term outcome.

Although the findings seem to underline the importance of heart rate control, the study has numerous limitations. Most importantly, it was not randomized. Numerous adjustments by multivariate analysis were made for age, gender, several cardiac risk factors, dobutamine stress echocardiography test results, and statin and angiotensin-converting enzyme inhibitor medication. No exact information was provided for individual groups on type and duration of surgery, type of anesthesia, type of primary endpoint, and follow-up time.

A recently published meta-analysis of 10 trials showed that strict control of heart rate (maximum perioperative heart rate of 99 beats per minute) was associated with a decreased risk of perioperative myocardial infarction, but at the expense of an increased risk for heart failure and bradycardia [16]. However, this meta-analysis looked only at the risk of myocardial infarction, and four of the 10 analyzed trials were not blinded. Another meta-analysis could not confirm strict heart rate control to be an independent predictor of outcome during perioperative beta-blocker therapy [17]. Furthermore, a subgroup sensitivity analysis within the meta-analysis of Bangalore *et al.* [14] did not detect a significant interaction between mean maximum heart rate and efficacy of beta-blocker therapy.

A very recent randomized controlled trial investigated the effectiveness and safety of perioperative beta-blocker and statin therapy on 30-day postoperative cardiac outcome in intermediate-risk patients undergoing non-cardiovascular surgery [18]. Bisoprolol was titrated to a perioperative heart rate of between 50 and 70 beats per minute. Patients receiving bisoprolol had a lower incidence of perioperative cardiac death and non-fatal myocardial infarction than control patients (2.1% versus 6.0%, HR 0.34, 95% CI 0.17-0.67; $P = 0.002$). Although these findings suggest that tight perioperative heart rate control is an essential part of perioperative beta-blocker therapy, they remain inconclusive because the study was statistically underpowered. *A priori* power analysis indicated that 1,500 patients would be required. However, ultimately only 533 patients were included in the bisoprolol group.

In a retrospective cohort study that looked at 30-day postoperative cardiac outcome in intermediate- and low-risk patients receiving beta-blockers perioperatively, mean preoperative heart rate was significantly higher in patients who died within 30 days of surgery than in those who survived (86 versus 70 beats per minute; $P = 0.03$) [19]. This finding points to a possible role of preoperative beta-blocker dose titration on the basis of heart rate response.

American College of Cardiology and American Heart Association guidelines

The strength of a particular recommendation for a treatment option can be judged by the class of recommendation and the level of evidence (LOE) on which the recommendation is based (Table 1). The updated guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) on perioperative cardiovascular evaluation [20,21] strongly recommend (class I recommendation) perioperative beta-blocker therapy in two situations: (a) continuation of beta-blockers in patients receiving them to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA class I guideline indications (LOE C) and (b) patients undergoing vascular surgery at

Table 1. Definitions of classes of recommendations and levels of evidence

Classes of recommendation	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
- Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
- Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful
Levels of evidence (LOEs)	
LOE A	Data derived from multiple randomized clinical trials or meta-analyses
LOE B	Data derived from a single randomized clinical trial or large non-randomized studies
LOE C	Consensus of opinion of the experts and/or small studies, retrospective studies, or registries

high cardiac risk owing to the finding of myocardial ischemia on perioperative testing (LOE B). Perioperative beta-blocker therapy is probably recommended (class IIa recommendations, LOE B) for patients undergoing vascular surgery in whom preoperative assessment identifies coronary artery disease, in whom preoperative assessment for vascular surgery identifies high cardiac risk (as defined by the presence of more than one clinical risk factor), and in whom preoperative assessment identifies coronary artery disease or high cardiac risk (as defined by the presence of more than one clinical risk factor) prior to intermediate-risk or vascular surgery.

The just-published European Society of Cardiology guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery [22] list the following recommendations for perioperative beta-blocker therapy:

Class I recommendations: patients (a) having known coronary artery disease or myocardial ischemia according to preoperative stress testing (LOE B), (b) scheduled for high-risk surgery (LOE B), and (c) having previously been treated with beta-blockers because of coronary artery disease, arrhythmias, or hypertension (LOE C).

Class IIa recommendations: patients (a) scheduled for intermediate-risk surgery (LOE B) and (b) previously having been treated with beta-blockers because of chronic heart failure with systolic dysfunction (LOE C).

Class IIb recommendation: patients scheduled for low-risk surgery with risk factor(s) (LOE B).

Class III recommendations: (a) high-dose beta-blockers without titration (LOE A) and (b) patients scheduled for low-risk surgery without risk factor(s) (LOE B).

It is further stated that 'treatment should be initiated optimally between 30 days and at least 1 week before surgery' and targeted heart rate and systolic blood pressure should be 60-70 beats per minute and greater than 100 mm Hg, respectively. Interestingly, for this recommendation, the class of recommendation and LOE are not provided.

Implications for clinical practice

The POISE study [9] is the first perioperative beta-blocker study with an adequate number of patients (75 times the number of patients included in the non-blinded DECREASE study) and events. It documents, on the one hand, the beneficial effect of routine perioperative beta-blocker therapy as reflected by a decrease in the incidence of perioperative non-fatal myocardial infarctions. It equally documents that routine perioperative beta-blocker therapy may carry considerable problems by increasing the risks for death and stroke. The POISE study highlights (a) the importance and need for large randomized trials in the perioperative setting and (b) the risk of assuming that an effective treatment regimen can have substantial benefit without carrying the potential for substantial harm. Patients may be unwilling to accept the increased risks of disabling stroke associated with perioperative beta-blocker therapy but be willing to accept the increased risk of non-fatal myocardial infarction associated with the lack of perioperative beta-blocker therapy.

Surely, the results of the POISE study cannot be interpreted as a general *pro* or *con* for perioperative beta-blocker therapy. However, they clearly show that it is generally not justified to start a fixed beta-blocker protocol preoperatively, even in patients with cardiac risk factors undergoing surgery associated with increased cardiac risk. It needs to be emphasized that the findings apply only to newly started beta-blocker therapy. Chronic beta-blocker therapy for symptomatic cardiovascular disease or secondary cardiovascular prevention must not be interrupted in the perioperative period [13].

The importance of strict heart rate control in the context of perioperative beta-blocker therapy as an independent predictor of outcome remains open to debate. From a physiological and pathophysiological standpoint, it is difficult to imagine how strict heart rate control *per se* can be expected to be of predictable benefit in the perioperative setting. There are numerous reasons for the development of perioperative tachycardia apart from myocardial ischemia (for example, hypovolemia, anemia, hypothermia, inadequate pain relief, latent heart failure, and developing sepsis). Each of these requires markedly different therapeutic interventions, and in none of these conditions is administration of beta-blockers a first-choice therapy. A 'one-therapy-fits-all approach' (that is, uniform heart rate control by beta-blockers) will predictably harm a certain high percentage of patients. Heart rate control by beta-blockers blunts compensatory cardiovascular mechanisms that might, however, be vital in the perioperative period to satisfy the frequently increased perioperative cardiovascular demands. It is time to change the paradigm from routinely administering beta-blockers to all patients with risk factors for adverse perioperative cardiac outcome to one of administering beta-blockers only when the indication has been clearly established and the effects of therapy can be closely monitored [23].

Conclusions

Given the results of the POISE study [9] and the recent meta-analysis by Bangalore *et al.* [14], most of the recommendations for perioperative beta-blocker therapy are no longer supported by evidence and require revision. Only the recommendation to continue beta-blockers in patients taking them for symptomatic cardiovascular disease remains unchallenged. It remains to be seen whether there will be, after all, a subgroup of patients who may benefit from perioperative beta-blocker therapy. Controversy will continue until the issues regarding choice and dosage of beta-blocker, timing (start and duration), and monitoring of beta-blocker therapy are settled.

Abbreviations

ACC, American College of Cardiology; AHA, American Heart Association; CI, confidence interval; CR, controlled release; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; HR, hazard ratio; LOE, level of evidence; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio; POISE, PeriOperative ISchemic Evaluation.

Competing interests

The author declares that he has no competing interests.

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