Perioperative Beta-Blockers in the Prevention of Perioperative Myocardial Infarction in non-Cardiac Surgery

Systematic Review and Meta-Analysis

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List of Abbreviations

Abb.	Full term
ACC	*American College of Cardiology*
ACS	*Acute Coronary Syndrome*
AHA	*American Heart Association*
ATP	*Adenosine Triphosphate*
BMI	*Body-Mass Index*
CAD	*Coronary Artery Disease*
CARP	*Coronary Artery Revas-cularization Prophylaxis*
CPGs	*Clinical Practice Guidelines*
DCI	*Dichloroisoproterenol*
DECREASE	*Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo*
ECG	*Electrocardiogram*
ICI	*Imperial Chemical Industries*
ISA	*Intrinsic Sympathomimetic Activity*
MI	*Myocardial Infarction*
MSA	*Membrane-Stabilizing Activity*
NSTEMI	*Non–ST-Segment Elevation MI*
PMI	*Perioperative Myocardial Infarction*
POISE	*Perioperative Ischemic Evaluation*
STEMI	*ST-Segment Elevation MI*
WHO	*World Health Organization*

Abstract

We searched Pubmed and Embase for randomised controlled trials investigating the use of β blockers in non-cardiac surgery. We extracted data for 30-day all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, heart failure, and myocardial ischaemia, safety outcomes of perioperative bradycardia, hypotension, and bronchospasm 33 trials included 12 306 patients. β blockers were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure, but were associated with a decrease (odds ratio [OR] 0·65, 95% CI 0·54–0·79) in non-fatal myocardial infarction (number needed to treat [NNT] 63) and decrease (OR 0·36, 0·26–0·50) in myocardial ischaemia (NNT 16) at the expense of an increase (OR 2·01, 1·27–3·68) in non-fatal strokes (number needed to harm [NNH] 293). The beneficial effects were driven mainly by trials with high risk of bias. For the safety outcomes, β blockers were associated with a high risk of perioperative bradycardia requiring treatment (NNH 22), and perioperative hypotension requiring treatment (NNH 17). We recorded no increased risk of bronchospasm.

Evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery. β blockers seem to increase the risk of stroke and possibly all-cause mortality but decrease the risk of non-fatal myocardial infarction. In view of the increased risk of stroke, bradycardia, and hypotension (which were independent predictors of death in the POISE trial), β blockers should not be routinely used for perioperative treatment of patients undergoing non-cardiac surgery unless patients are already taking them for clinically indicated reasons (heart failure, coronary artery disease, previous myocardial infarction.

Keywords: Electrocardiogram – Dichloroisoproterenol - Coronary Artery Revas-cularization Prophylaxis

INTRODUCTION

More than 230 million major surgeries are performed annually worldwide ***(Weiser et al., 2008)*** and this number grows continuously. The 30-day mortality associated with moderate- to high-risk noncardiac surgery in recent large cohorts and population-based studies exceeds 2% and surpasses 5% in patients at high cardiac risk ***(Fleisher et al., 2007).*** Cardiac complications constitute the most common cause of postoperative morbidity and mortality, having considerable impact on the length and cost of hospitalization ***(Mackey et al., 2006).*** As our population ages, more high-risk cardiac patients will undergo surgery, and perioperative myocardial infarction (PMI) can be an increasing problem.

Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with non-cardiac surgery. Prevention of a PMI is thus a prerequisite for an improvement in overall postoperative outcome. The aetiology of PMI is multifactorial. The perioperative period induces large, unpredictable and unphysiological alterations in coronary plaque morphology, function and progression, and may trigger a mismatch of myocardial oxygen supply and demand. With many diverse factors involved, it is unlikely that one single intervention will successfully improve cardiac outcome following non-cardiac surgery ***(Fleisher et al., 2006).***

Traditionally, MI was defined by the World Health Organization criteria, ECG criteria, and cardiac enzymes. Defining PMI, however, is often difficult because most PMIs occur without symptoms in anesthetized or sedated patients, ECG changes are subtle and/or transient, and the creatine kinase-MB isoenzyme has limited sensitivity and specificity because of coexisting skeletal muscle injury ***(Wu et al., 2007).*** Consequently, PMI was often recognized late (postoperative day 3 to 5), resulting in high mortality (30% to 70%) ***(Lindenauer et al., 2005).***

Cardiac troponin assays have changed this definition ***(Jaffe, 2003).*** The recent universal definition of MI ***(Thygesen et al., 2007)*** is based on a rise and/or fall of cardiac biomarkers (preferably troponin) in the setting of myocardial ischemia: cardiac symptoms, ECG changes, or imaging findings. Studies using serial troponin measurements demonstrate that most PMIs start within 24 to 48 hours of surgery during the greatest postoperative stress ***(Erasmus et al., 2012; Kikura et al., 2008). Le Manach et al. (2005)*** observed early (<24 hours) and late (>24 hours) peaks in troponin in 1136 patients after abdominal aortic aneurysmectomy. Yet, 90% of troponin elevations began within <24 hours.

A multifactorial, step-wise approach is indicated. Based on increasing knowledge of the nature of atherosclerotic coronary artery disease, and in view of the poor positive predictive value of non-invasive cardiac stress tests, and the

considerable risk of coronary angiography and coronary revascularization in high-risk patients, the paradigm is shifting from an emphasis on extensive non-invasive preoperative risk stratification to a combination of selective non-invasive testing and aggressive pharmacological perioperative therapy. Perioperative plaque stabilization by pharmacological means may be as important in the prevention of PMI as an increase in myocardial oxygen supply or a reduction in myocardial oxygen demand perioperative beta blockade was recommended for a fairly broad spectrum of surgical patients in initial versions of the American College of Cardiology (ACC)/American Heart Association (AHA) clinical practice guidelines (CPGs). For example, among patients with untreated hypertension, known coronary artery disease, or cardiac risk factors, perioperative beta blockade received a Class II recommendation in 1996 ***(Poldermans and Devereaux, 2009)*** and a Class IIa recommendation in 2002 ***(Mackey et al., 2006).*** Nonetheless, for several reasons, the strength and scope of these recommendations diminished over successive iterations of these CPGs ***(Erasmus, 2011).*** First, subsequent moderate-sized RCTs failed to demonstrate significant benefits from beta blockade ***(Thygesen et al., 2007).*** Second, in the POISE-1 trial of almost 9000 participants, it was found that although perioperative beta blockade prevented perioperative MI, this benefit was accompanied by increased rates of death, stroke, hypotension, and bradycardia ***(Kikura et al., 2008).*** Although the POISE-1 trial has been criticized for starting long-acting

beta blockers at high doses shortly prior to surgery ***(Fleisher et al., 2009),*** its results highlighted the potential for important risks from perioperative beta blockade. Third, the validity of work led by Poldermans, including 2 influential perioperative beta-blockade RCTs ***(Le Manach et al., 2005),*** has been scrutinized because of concerns about scientific misconduct ***(Dunkelgrun et al., 2009; Juul et al., 2006).*** Consequently, it has been suggested that CPGs re-evaluate and potentially exclude these data from the evidence base used to inform recommendations about perioperative beta blockade ***(Eagle et al., 2002).***

Based on previous introduction the benefit of use of preoperative beta blockers to prevent PMI is still confusing with the need of further systematic reviews and metaanalysis to help conducting new evidence based practice ***(Bouri et al., 2014).***

AIM OF THE WORK

Objective:

The aim of this work is to conduct a systematic review and meta-analysis to search the value of Perioperative beta-blockers in the prevention of perioperative myocardial infarction in non-cardiac surgery.

Hypothesis

Use of perioperative beta-blockers can reduce the incidence of PMI and cardiac related morbidity and mortality following non cardiac surgery.

Research question:

Does the Use of perioperative beta-blockers can reduce the incidence of PMI and cardiac related morbidity and mortality following non cardiac surgery?

Chapter 1
MYOCARDIAL INFARCTION

Myocardial infarction (MI) (ie, heart attack) is the irreversible death (necrosis) of heart muscle secondary to prolonged lack of oxygen supply (ischemia). Approximately 1.5 million cases of MI occur annually in the United States.

Myocardial infarction (MI) usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in an epicardial coronary artery, resulting in an acute reduction of blood supply to a portion of the myocardium.

Although the clinical presentation of a patient is a key component in the overall evaluation of the patient with MI, many events are either "silent" or are not clinically recognized by patients, families, and health care providers. The appearance of cardiac biomarkers in the circulation generally indicates myocardial necrosis and is a useful adjunct to diagnosis.

MI is considered part of a spectrum referred to as acute coronary syndrome (ACS). The ACS continuum representing ongoing myocardial ischemia or injury consists of unstable angina, non–ST-segment elevation MI (NSTEMI) collectively referred to as non–ST-segment acute coronary syndrome (NSTE ACS) and ST-segment elevation MI (STEMI). Patients with ischemic discomfort may or may not have ST-segment or