THE PERIOPERATIVE USE OF ß-BLOCKERS

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Perioperative myocardial infarction is a leading cause of postoperative morbidity and mortality (1). The etiology of postoperative MI is the subject of some debate but is thought to include prolonged ischemia resulting from tachycardia (2).

Perioperative blockade could prevent perioperative cardiac damage and improve long-term cardiac outcome in noncardiac surgical patients. The beneficial effects of ß-blockers on myocardial function have been widely described (3). Beta-blockers reduce myocardial oxygen consumption by decreasing heart rate and extending the time of diastole, allowing better coronary perfusion. Furthermore, they attenuate the excitotoxic effects of catecholamines (4).

The American College of Cardiology and American Heart Association guidelines on perioperative assessment recommend perioperative blockers for noncardiac surgery. The most marked effects are observed in high-risk patients undergoing vascular surgery

In cardiac surgery, the efficacy of ß-blockers is limited to the prevention of postoperative atrial fibrillation in coronary artery bypass graft (CABG) surgery, and only one observational analysis suggested a small but consistent survival benefit for patients receiving ß-blocker therapy and undergoing CABG surgery (5).

Beta-adrenergic antagonists bind selectively to the b-adrenoceptors producing a competitive and reversible antagonism of the effects of ß-adrenergic stimuli on various organs (Table 1). Their pharmacological effects can be explained from the knowledge of the responses elicited by these receptors in the various tissues and the activity of the sympathetic tone. Thus, ß-blockers

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have relatively little effect on heart rate and contractility in an individual at rest but slow heart rate and decrease cardiac contractility when the sympathetic nervous system is activated, i.e. during exercise or stres (6).

Table 1 Effects mediated by β_1- and β_2-adrenoceptors

Tissue	Receptor	Effect
Heart		
SA node	β_1, β_2	Increase in heart rate
AV node	β_1, β_2	Increase in conduction velocity
Atria	β_1, β_2	Increase in contractility
Ventricles	β_1, β_2	Increase in contractility, conduction velocity and automaticity of idioventricular pacemakers
Arteries	β_2	Vasodilation
Veins	β_2	Vasodilation
Skeletal muscle	β_2	Vasodilation, increased contractility Glycogenolysis, K^+ uptake
Liver	β_2	Glycogenolysis and gluconeogenesis
Pancreas (β cells)	β_2	Insulin and glucagon secretion
Fat cells	β_1	Lipolysis
Bronchi	β_2	Bronchodilation
Kidney	β_1	Renin release
Gallbladder and ducts	β_2	Relaxation
Urinary bladder detrusor	β_2	Relaxation
Uterus	β_2	Relaxation
Gastrointestinal	β_2	Relaxation
Nerve terminals	β_2	Promotes noradrenaline release
Parathyroid glands	β_1, β_2	Parathormone secretion
Thyroid gland	β_2	T4 → T3 conversion

SA: Sino-Atrial; AV: Auriculo-Ventricular.

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The indications of ß–blockers were as follows:

hypertension
Prophylaxis of stable angina attacks
tachyarrhythmias
After AMI treatment and prophylaxis (secondary prophylaxis)
hyperthyroidism
Hypertrophic obstructive cardiomyopathy
Chronic congestive heart failure
migraine
pheochromocytoma
glaucoma
Panic and anxiety
Portal hypertension

The contraindications to initiate ß-blocker treatment include asthma, symptomatic hypotension or bradycardia and severe decompensated heart failure. Contraindications may be relative, in patients in whom the benefit of therapy may outweigh the risk of untoward effects. Chronic obstructive lung disease without bronchospastic activity and peripheral vascular disease

are not considered as absolute contraindications and high risk patients may obtain a significant benefit from this therapy. Patients with heart failure and bradycardia due to sick sinus node or second or third degree AV-block may benefit from pre-treatment with pacemaker in order to tolerate ß-blockers, although this approach has, however, not been formally tested. Diabetes or intermittent lower limb claudication are not absolute contraindications for ß-blockers use.

Review of major randomized controlled trials of perioperative ß-blockade

The McSPI group trial included Veterans Affairs (VA) patients with, or at risk for, CAD undergoing non-cardiac surgery. Atenolol was used as the study drug. The primary outcome was all-cause mortality at 6 months and 1 and 2 yr with a secondary outcome of combined MI, unstable angina, congestive heart failure (CHF), myocardial revascularization, and/or death. The study showed significant benefits in both the primary and secondary endpoints. At 2 yr follow-up, mortality was significantly lower in the atenolol group (10% vs 21% in the placebo group) with a reduction in the incidence of postoperative cardiac events (7).

The first DECREASE trial examined patients with positive results on dobutamine stress echocardiography undergoing major vascular surgery. Patients were randomized to either standard perioperative treatment or bisoprolol. The study showed a significant reduction in its primary endpoint of composite death from cardiac causes or nonfatal MI within 30 days after operation (34% in the Standard care group vs 3.4% in the bisoprolol group) (8).

The POBBLE (Perioperative ß-Blockade) trial was a randomized double-blinded placebo-controlled trial of metoprolol in patients without CAD undergoing infrarenal vascularsurgery under general anaesthesia. Hospital stay was shorter in the metoprolol arm (10 compared with 12 days; P,0.02). More patients in the metoprolol group required intraoperative inotropic support (9).

In DIPOM, diabetic patients undergoing major non-cardiac surgery received sustained-release metoprolol 100 mg per day or placebo starting the day before surgery, continuing after operation to a maximum of 8 days. The mean duration of postoperative metoprolol or placebo intervention was 4.6 and 4.9 days, respectively. The primary outcome was composite of all-cause mortality, AMI, unstable angina, or CHF. However, they did find a significant increase in hypotension and bradycardia in the treatment group (10).

Metoprolol after Vascular Surgery (MaVS) was a double blinded randomized placebo-controlled trial did not show any clear benefit to perioperative b-blockade in vascular surgery patients, who were previously presumed to

benefit from this therapy (11).

The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study was a double blinded placebo-controlled multicentre trial evaluating the cardiovascular protective effects of 10 days of oral bisoprolol in patients having spinal anaesthesia (12).

POISE included 8351 patients with or at risk of atherosclerotic disease randomized to placebo or metoprolol succinate extended release (ER) 100 mg orally. The primary endpoint of the POISE trial mirrored other trials with a composite of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest at 30 days. Metoprolol reduced the primary endpoint A significant decrease in MI was largely responsible for the overall reduction in the primary endpoint. However, there was a significant increase in total mortality in the metoprolol group. Stroke incidence was 1% with metoprolol compared with 0.5% (13).

Esmolol

Esmolol is an ultra–short-acting ß-blocker, with a plasma half-life of approximately 2 minutes, a time to peak effect of about 6 to 10 minutes after administration, and a washout time considered to be 9 minutes after stopping infusion. All these properties suggest using this ß-blocker as the first-choice drug in critical patients in whom possible side effects such as cardiac failure, hypotension, or bradycardia cause a rapid and immediate interruption of drug administration. Usually, it is used as a loading dose followed by a continuous infusion. These clinically useful pharmacologic characteristics have led to the use of esmolol in the prevention of a sympathetic response in cardiac surgery.

The meta-analysis of Zangrillo et al. in 2009 showed that ultra–short-acting ß-blocker esmolol is probably the best choice of alpha-blocker in the perioperative period of patients undergoing cardiac surgery. In the studies included in the present meta-analysis, esmolol was used in 3 different clinical conditions: (1) preventing the hemodynamic response to some procedures (in particular extubation), (2) treatment and prophylaxis of atrial fibrillation at the end of CPB, and (3) administration during surgery (in many cases just before and during the cardioplegia) in order to reach or improve myocardial protection. Numerous studies showed how an increase of tachycardia is strongly connected to episodes of myocardial ischemia (14).

Another meta-analysis about esmolol use in non-cardiac surgery concluded that esmolol seemed to reduce the incidence of myocardial ischemia in non-cardiac surgery without increasing the episodes of hypotension and bradycardia (15).

To conclude:

- ß-blockers are protective against cardiac complications in high risk surgery
- the high and fixed doses of ß-blockers may be harmful due to its hypotensive effect
- esmolol reduces the incidence of myocardial ischemia and arrhythmias in cardiac surgery
- esmolol reduces myocardial ischemia in non-cardiac surgery without increasing the episodes of hypotension and bradycardia
- the important issue about ß- blockers is titration.

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