Perioperative β-adrenoceptor blockade in major non-cardiac surgery

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Summary
This review discusses the mechanisms of perioperative ischaemia and how β-adrenoceptor blockade may prevent it. The evidence for perioperative β-adrenoceptor blockers, their side effects and recommendations for their perioperative use are discussed.

Postoperative myocardial infarction (PMI) has an incidence of 5.6%[1] in patients with known ischaemic heart disease (IHD) and elective non-cardiac surgery. The pathophysiology of perioperative ischaemia may be different between intraoperative and postoperative ischaemia. Intraoperative ischaemia is more commonly associated with unstable, non-critical plaques, with complicating thrombus formation.[2] This may manifest as intra-operative ischaemia despite stable haemodynamics.[3]

In comparison, postoperative ischaemia is usually secondary to a myocardial oxygen supply-demand imbalance, characterized by prolonged periods of ST depression representative of subendocardial ischaemia, resulting in non-Q wave infarcts [1, 4]. Postoperative myocardial ischaemia increases the risk of an ischaemic associated cardiac event 9-fold (cardiac death, MI or unstable angina).[5] Increased duration of perioperative ischaemia (more than 30 minutes[6] or more than 2 hours[4]) and repetitive ischaemia[7] are associated with a poor cardiac outcome.

The beneficial effects of β-adrenoceptor blockade

β-adrenoceptor blockers are theoretically beneficial in preventing both intraoperative and postoperative myocardial ischaemia. Mechanisms include;

1. Optimizing myocardial oxygen supply-demand balance. β-adrenoceptor blockade decreases myocardial oxygen demand by decreasing heart rate (HR) and inotropy, and increases supply by decreasing myocardial oxygen consumption and increasing the time for myocardial perfusion. The HR at which the myocardium becomes ischaemic is not absolute and must be individualized, however a tachycardia per se, increases the size of an infarct.[8]
2. Plaque rupture. β-adrenoceptor blockade decreases the stiffness of atherosclerotic plaques which increases their strength, while decreasing the shear forces across the plaques.[9] An increased HR may further traumatize and activate platelets across the coronary bed.[8]
3. Arrhythmias. Sympathetic tone is important in ventricular and atrial arrhythmias and β-adrenoceptor blockers shift the autonomic balance towards vagal dominance.[10,11]
4. Beta receptor selectivity (β-1 versus β-2 stimulation). Catecholamine mediated cardiomyocyte death is a function of β-1 and not β-2 adrenoceptor stimulation. Indeed β-2 stimulation may protect the cardiomyocyte from apoptosis-inducing stimuli.[8] β-2 receptor stimulation enhances both diastolic and systolic cardiac function, without developing overt cardiomyopathy.[8] This may partially explain why β1-selective adrenoceptor blockers improve survival in the failing heart.[12] β-1 adrenoceptor blockade may also enhance β-2 stimulation.[8]

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A historical perspective of perioperative β-adrenoceptor blockade

Currently β-adrenoceptor blockade is considered the sole proven pharmacological means of reducing perioperative short and long-term cardiovascular morbidity and mortality.[8]

In 1985, Slogoff and Keats showed two important relationships in patients presenting for CABG; the association between ischaemia and PMI and the association between tachycardia and PMI.[3] Subsequently, perioperative β-adrenoceptor blockade studies were to show a significant decrease in both perioperative HR and ischaemia.

Pasternack in a case-control study, showed with preoperative oral metoprolol and postoperative intravenous metoprolol a significant decrease in PMI and arrhythmias in patients undergoing abdominal aortic aneurysm repair.[13]

Stone and colleagues in a randomized controlled trial gave hypertensive patients a single oral dose of atenolol 2 hours prior to surgery.[14] This significantly decreased myocardial ischaemia on ECG during intubation and emergence. Importantly, tachycardia (and not blood pressure variation) was always associated with ischaemia. The number needed to treat (NNT) to prevent myocardial ischaemia was 3.8.

In 1989, Pasternack's group in a case-control study of patients for peripheral vascular surgery, showed that patients treated with oral metoprolol immediately prior to induction had significantly less intraoperative silent ischemia, both in frequency and duration and a significantly lower intraoperative HR.[15]

Yaeger's retrospective case-control study in 1995 of patients undergoing major peripheral vascular surgery[16], showed that patients receiving perioperative β-adrenoceptor blockade had a 50% reduction in the relative risk of PMI (NNT 5).

It was Mangano's study published in 1996[17], which changed practice recommendations.[18] Despite a large amount of criticism, it

was the first randomized trial, which examined clinical end points (primary outcome was mortality from all causes within two years of discharge, with secondary outcomes of MI, unstable angina, congestive cardiac failure (CCF), myocardial revascularization and death). Patients with IHD or considered to be at risk of coronary artery disease (CAD) scheduled for elective non-cardiac surgery were randomized to receive intravenous atenolol or placebo immediately preoperatively with continuance of β-adrenoceptor blockade upto 7 days postoperatively, with the goal of titrating the HR to between 55 and 65 bpm. The outcome was a 55% reduction in cardiac mortality (NNT 12.5) and 65% reduction in 2 year overall mortality (NNT 8.3).

The study was criticized for a higher preponderance of IHD and diabetes in the placebo group, more patients in the treatment group been on β-adrenoceptor blockers and ACE inhibitors, no in hospital difference in MI or cardiac morbidity, the difficulty in assigning a causal relationship to perioperative β-adrenoceptor blockers and long-term survival, unknown interventions between surgery and two years post surgery and the possible role chronic β-adrenoceptor blocker withdrawal on patient mortality in the placebo group.[19-22]

A second paper from this group in 1998[23], showed similar intraoperative ischaemia between perioperative β-adrenoceptor blockade and placebo groups, but significantly decreased ischaemia in the first 48 hours after surgery in the β-adrenoceptor blockade group (NNT 6.7). Patients who experienced ischaemia were also more likely to die in the next 2 years.

In the same year Raby and colleagues, in a prospective randomized trial of vascular surgery patients, identified pre-operative ischaemia (ST depression for more than a minute) with Holter monitoring.[24] The minimum HR for ischaemia (defined as the ischaemic threshold) was identified. These patients were randomized to receive esmolol or placebo infusions for 48 hours postoperatively with the goal of maintaining the HR 20% below this ischaemic threshold. The esmolol group had significantly fewer ischaemic patients (NNT 2.5), less ischaemic events and a shorter duration of ischaemia. Univariate predictors of myocardial ischaemia resolution included esmolol and achieving target HR. Achieving target HR was a multivariate predictor.[24]

Poldermans in 1999 randomized high-risk patients (presence of both clinical risk factors and dobutamine inducible wall motion abnormalities) undergoing abdominal and infrainguinal vascular surgery to β-adrenoceptor blockade from one week prior to surgery until 30 days postoperatively.[25] This study was halted due to a 5-fold decrease in 30 day perioperative death (NNT 7.4) and 10-fold decrease in adverse cardiac events (NNT 6.3).

Two subsequent studies were to highlight possible limitations of the beneficial effects of perioperative β-adrenoceptor blockade.[26,27]

In a randomized controlled trial, Urban' group administrated prophylactic esmolol infusions immediately following surgery, followed by metoprolol for 48 hours to maintain a HR of less than 80, in patients undergoing elective total knee arthroplasty with epidural anaesthesia.[26] There was a significant difference in number of patients with ischaemic events, number of ischaemic events, and duration of ischaemic events. There was no significant difference in postoperative ischaemia, MI or cardiac events. This was attributed to the fact that this was an intermediate risk group and 240 patients would need to be treated to show a significant difference in cardiac outcome.[26] A target HR of 80 bpm may be too high to contribute to mortality reduction[28], as other studies, which showed improved survival, targeted a lower HR.[17,23]

Boersma and colleagues[27] showed that in patients on β-adrenoceptor blockers (both chronic administration and perioperative randomization) undergoing high-risk surgery, the absence of any additional cardiac risk factors according to Lee's Revised Risk Index[29] revealed little additional benefit from perioperative β-adrenoceptor blockade. However at the other extreme, patients with three of more additional cardiac risk factors and extensive stress induced wall motion abnormalities, had significantly increased cardiac death and MI, even if randomized to b-adrenoceptor blockade. This subgroup of patients should receive further risk stratification and management prior to surgery.[27]

Side effects of β-adrenoceptor blockade

While a high-grade conduction block remains an absolute contraindication to β-adrenoceptor blockade, other side effects and relative contraindications are more controversial.

Side effects with chronic β-adrenoceptor blockade are common and upto a third of these patients are non-compliant due to side effects.[30]

Bradycardia is the most commonly reported complication of β-adrenoceptor blockade with a number needed to harm (NNH) of 4.3.[14,17] Intervention may be required in upto 50% of patients experiencing this complication.[14]

Bronchospasm is more controversial with a reported NNH of between 16 and 118.[30,31] The incidence of perioperative bronchospasm has not been reported to increase in the perioperative period when used in high-risk patients[17,23,24,27], although a number of studies have excluded patients with bronchospastic disease.[14,25,26]

Although beta blockade administration has been shown to be beneficial in acute MI[31] and chronic cardiac failure[12], perioperative β-adrenoceptor blockade has not been studied specifically in patients with a depressed ejection fraction in the perioperative period[28] and in some studies a significantly depressed ejection fraction (<30%) was an exclusion criterion.[26] Clarification of this subgroup is required in the perioperative period.

In peripheral vascular disease (PVD), the HOT study showed no worsening of PVD with β-adrenoceptor blockade[32], although 4.2% of patients experienced increased claudication or cold feet with β-adrenoceptor blockade in the UKPDS trial.[30]

Most clinicians would consider the small rise in cholesterol associated with b-adrenoceptor blockade acceptable when weighed against their cardioprotective effects.[33]

β-adrenoceptor upregulation and possible myocardial ischaemia and infarction is a concern with β-adrenoceptor blocker withdrawal in the postoperative period. β-adrenoceptor blocker discontinuation immediately post surgery, markedly increases the risk of PMI and death.[34] This has been associated with withdrawal after long-term β-adrenoceptor blocker administration[35] and abrupt withdrawal as opposed to a titrated three-day withdrawal.[36] In the perioperative β-adrenoceptor blocker studies this has not been shown despite administration upto thirty days postoperatively.[17,25]

Recommendations

The present recommendations for perioperative β-adrenoceptor blockade are as described by Mangano.[17,18] This is the only trial which used a sufficiently wide range of different surgical specialties while randomizing patients to clinical end points.

Patients eligible for perioperative β-adrenoceptor blockade had or were at risk of CAD and were undergoing high-risk surgery. The presence of CAD is defined as having had a previous MI, typical angina or atypical angina with a positive stress test. To be considered at risk of CAD, one should have at least two of the following;

age of more than 65 years, current smoker, cholesterol of more than 6.2mmmol/L and / or diabetes.[17] High-risk surgery included major vascular, intra-abdominal, orthopaedic, neurosurgical, intrathoracic, head and neck and plastics.[17]

More recent studies have illustrated that these criteria maybe too broad.[26,27] In patients undergoing high-risk surgery, three groups of patients may be defined preoperatively[27] using Lee's Revised Cardiac Index[29], where a point is scored for age more than 70 years, current angina, prior MI, prior CCF, prior CVA, diabetes and renal failure.

If no additional points are scored, β-adrenoceptor blockade offers little additional benefit (1.2% versus 0% adverse cardiac events).[27] With one to two points, β-adrenoceptor blockade decreases the risk of adverse cardiac events from 3% to 0.9%.[27] With three or more points, all patients benefit from β-adrenoceptor blockade, with the exception of the subgroup of patients with extensive ischaemia induced wall motion abnormalities (more than 5 segments by definition). All patients with three or more points require further risk stratification, to identify this high-risk group.[27]

The administration of β-adrenoceptor blockers to the intermediate group (1 to 2 points) is controversial, if CAD is not proven.[37] In this scenario a risk-benefit analysis is advocated.[37] This should consider the NNT to prevent an adverse perioperative cardiac event against the NNH for a specific individual.

A meta-analysis of all the prospective randomized studies[28] reported the NNT to prevent perioperative myocardial ischemia as 2.5-6.7 and to decrease cardiac or all-cause mortality as 3.2-8.3. The most marked effects were seen in patients considered to be at high risk for perioperative cardiac events.

The risk of adverse perioperative cardiac events can be predicted from Lee's Revised Cardiac Index.[29] In patients undergoing high-risk surgery, the risk of major cardiac complications with 1, 2 and 3 additional points is 0.9-1.3%, 4-7% and 9-11% respectively. Major cardiac complications include MI, pulmonary oedema, ventricular fibrillation, primary cardiac arrest and complete heart block.[29]

The question of balancing risks is well illustrated in the following example by Howell and Sear.[37] In a diabetic undergoing high-risk surgery, the risk of cardiac complications approximately 1.1%[29], which would require more than 180 treatments to halve this complication rate.[37] Whether this is safe and effective practice is controversial and auditing and publishing of one's own practice in this group is strongly advocated, particularly as all the trials have taken place in an environment of intensive monitoring during the period of β-adrenoceptor blockade, minimizing the risk of potentially serious side effects. Unfortunately, this is not the case in every day practice.[37]

Cardioselective agents. All the published studies have used cardioselective β-adrenoceptor blockers, which is logical in an attempt to minimize undesirable side effects.[28]

Dose. Titration of the dose to a target HR prior to induction of anesthesia is recommended.[28] Mangano's target HR was 55 to 65 bpm1[7,23] and Raby's was 20% below an ischaemic threshold.[24] Dosing in Mangano's team was dependent on HR and BP.[17] Treatment was withheld if HR was less than 55 bpm or SBP was less than 100mmHg. Full therapy (10mg atenolol intravenously or 100mg atenolol orally), was given if the HR was more than 65 bpm and SBP more than 100mmHg. Patients between these two groups were given half the dose. If intravenous atenolol was used it was administered every 12 hours and oral atenolol every 24 hours. Indeed it has been suggested that a HR of 80 bpm[26], may be too high to offer maximal myocardial protection[28], despite the fact that all ischaemic episodes in this study occurred at a HR of more than 80 bpm.[26]

Duration of therapy. Differences in treatment protocols leave questions unanswered regarding optimal duration of therapy[28], both preoperatively and postoperatively. In the preoperative period the degree of sympathetic blockade necessary to offer myocardial protection is unknown.[24] If one is using oral agents immediately preoperatively, in order to achieve therapeutic levels a drug with a short half-life eg metoprolol is logical[22], however atenolol orally two hours pre-operatively has been shown to decrease perioperative ischaemia.[14] Should β-adrenoceptor blockade administration start long before surgery, some patients may ultimately receive unnecessary β-adrenoceptor blockade if surgery is subsequently cancelled.[22] This problem may be circumvented by using intravenous atenolol in the immediate preoperative period, where target HR control may be achieved within 10 minutes of administration.[17]

Postoperatively, patients should be covered at least for the period associated with the highest risk of PMI. The majority of PMI occur within the first 72 hours postoperatively, and almost all within 96 hours of surgery.[1] Thus one should consider a minimum of at least 96 hours of postoperative β-adrenoceptor blockade. The only prospectively randomized trials shown to decrease mortality have all had b-adrenoceptor blockade administered for more than 96 hours[17,23,25], with seven days been the minimum administration period. However, a case-control study suggests that a shorter period of postoperative administration may still decrease mortality.[16]

The patient considered at risk of adverse β-adrenoceptor blocker complications. In the patient where β-adrenoceptor blockade is indicated, but real concerns exist regarding side effects, esmolol is a good agent to check for efficacy and side effects. If esmolol administration is satisfactory, then it would be reasonable to institute oral β-adrenoceptor blockade.[38]

Emergency surgery. Currently there are no studies in this group, as concerns exist about hypovolaemia, haemorrhage and sepsis complicating β-adrenoceptor blockade.[39]

Does chronic β-adrenoceptor blockade afford similar protection?

In general surgical patients, chronic β-adrenoceptor blockade has failed to show a positive effect on perioperative silent ischaemia and cardiac mortality upto a year postoperatively.[40-43]

Indeed in Sprung's study, chronic β-adrenoceptor blockade was associated with an increased PMI.[44] Chronic β-adrenoceptor blockade may be a marker of more severe disease and hence, a worse outcome.[44] However HR targeting with β-adrenoceptor blockers in the perioperative period still improves outcome in these patients when correctly selected.[17,23]

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