Perioperative beta blockade: a practice in need of optimisation

Lawson RB, MBBCh
Department of Anaesthesia, University of the Witwatersrand, Johannesburg
Correspondence to: Dr R Lawson, e-mail: drlawson@yahoo.co.uk

Introduction

As anaesthetists, one of our primary objectives is to prevent complications in the perioperative period. Cardiovascular complications, in particular, are a leading cause of morbidity and mortality. The introduction of beta blocker medication around the time of major non-cardiac surgery continues to be one of the most controversial practices in perioperative medicine. The practice targets a reduction in the incidence and severity of major cardiovascular events.

Number of patients at risk of a major perioperative cardiac event

A provisional estimate suggests that in excess of 200 million major surgical procedures are undertaken worldwide every year. Cardiac death has an incidence of 0.5–1.5%, and major cardiovascular complications during the perioperative period affect 2–3.5% of all patients undergoing major non-cardiac surgery.

Feasibility of beta blockade as an intervention

Major perioperative cardiac events are the result of perioperative myocardial infarction (PMI), congestive heart failure and arrhythmia. Adverse events are associated with episodes of myocardial ischaemia, and these episodes occur most frequently in the immediate postoperative period, at times of high physiological stress. PMI is a powerful independent predictor of mortality and is the commonest cause of perioperative cardiac death.

The understanding of the pathophysiology of PMI remains incomplete. Plaque rupture and imbalance between myocardial oxygen supply and demand are the two processes thought to be involved.

The majority of PMIs occur within 24–48 hours of surgery. Catecholamine levels continue to rise during this period. The immediate beneficial effects of beta blockers administered in this setting are not restricted to the control of heart rate. Attenuation of the cardiotoxic effects of catecholamines limits the increase in myocardial oxygen demand related to heart rate, contractility and increased systolic blood pressure. The anti-arrhythmic properties of beta blockers are a further favourable effect. Oxygen supply is enhanced by prolongation of diastole and possibly by an improved distribution of coronary blood flow to the subendocardium. Vessel patency is promoted by a reduction in shear stresses across atherosclerotic plaque, and centrally mediated inhibition of platelet aggregation.

Ventricular remodelling with improved coronary flow reserve, changes in myocardial gene expression and a number of anti-inflammatory effects are potential delayed benefits of perioperative beta blockade. Lower levels of C-reactive protein, in patients with coronary artery disease treated with beta blockers, imply a reduction in inflammation. Anti-inflammatory effects may play a role in the stabilisation of atherosclerotic plaque.

Assessment of risk

Methods of predicting which patients are likely to suffer complications have become an important focus in modern day anaesthesia. The Revised Cardiac Risk Index remains the most widely accepted patient risk stratification tool. It is also necessary to assess the risks related to the surgical procedure itself. Identifying patients at higher risk for adverse events allows a more accurately targeted approach to intervention.

Review of the evidence

The pre-POISE era

In the early 1970s, it was not uncommon for beta
blocker medication to be withheld before surgery.\textsuperscript{23} A small study demonstrating beneficial effects of beta blockers at the time of laryngoscopy\textsuperscript{24} resulted in a gradual increase in the number of patients continuing beta blocker medication in the perioperative period.

Although no longer recognised as first line therapy for hypertension, the utility of beta blockers in the secondary prevention of ischaemic events in patients with ischaemic heart disease (IHD), and their role in the management of congestive heart failure, has led to an increase in the number of patients presenting for surgery with a medical indication for continued use. Not only is it thought safe practice to continue beta blockers in the perioperative period, but it is apparent that withdrawal of beta blockers around the time of surgery is, in fact, harmful.\textsuperscript{25,26}

Initial interest in the use of beta blockers as a cardiovascular risk modification tool arose in the late 1980s.\textsuperscript{27-29} However, it was the publication of two randomised controlled trials towards the end of the 20th century that accelerated development in the field. The Multicenter Study of Perioperative Ischemia Research Group (MCSP), under Mangan, published results in 1996.\textsuperscript{30} The investigators claimed favourable effects of atenolol on the intermediate term outcome in patients with, or at risk for, coronary artery disease. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) investigators, led by Poldermans in 1999, demonstrated such an impressive reduction in mortality and perioperative myocardial infarction in patients treated with bisoprolol, that the trial was discontinued early.\textsuperscript{31} The results of these two trials forged expert opinion through the early part of the 21st century. The limitations of these trials were widely publicised, and yet the findings were accepted by many with great enthusiasm.\textsuperscript{32}

The practice of perioperative beta blocker therapy developed rapidly, and was soon endorsed by expert consensus guidelines.\textsuperscript{33} A 2001 critical analysis of supporting evidence for patient safety initiatives identified perioperative beta blockade in selected patients as one of the 11 most highly rated practices across all fields of medicine.\textsuperscript{34} Scientists were so impressed that research interests broadened to include patient groups outside of those that had previously shown benefit. The expansion occurred, despite an understanding that these recommendations were based on underpowered studies with potential methodological weaknesses.

In contrast, uncertainty among clinicians escalated, as a number of studies were unable to reproduce the findings of Mangano and Poldermans.\textsuperscript{35-37} More importantly, significant concerns were raised about an increased risk of bradycardia and hypotension.\textsuperscript{36-38}

Despite the premature introduction of quality of care initiatives at many hospitals across the United States\textsuperscript{39}, the initiation of beta blockers in the perioperative period remained an under-utilised strategy.\textsuperscript{40,41} This may reflect a lack of clinician confidence in the true benefit of the practice across all national guideline recommendations. Concern for the potential adverse effects of beta blockers continues to be a major obstacle to widespread implementation of these guidelines.

The POISE trial and beyond

A large multi-centre, randomised controlled trial was needed to help to clarify best practice. As the largest randomised controlled trial ever conducted in the field, the POISE trial\textsuperscript{42} was expected to deliver the final verdict on perioperative beta blockade.

The primary endpoint measure in POISE was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest. Administration of metoprolol 2–4 hours before surgery, and continued for 30 days, demonstrated a decreased risk in the primary endpoint (hazard ratio 0.84, 95% confidence interval 0.70–0.99; p-value = 0.0399) and a decreased risk of perioperative myocardial infarction (HR 0.73, 95% CI 0.60–0.89; p = 0.0017). But, the trial also revealed an increased risk for all cause mortality (HR 1.33, 95% CI 1.03–1.74; p = 0.0317) and cerebrovascular accident (HR 2.17, 95% CI 1.26–3.74; p = 0.0053).

For every 1 000 patients in the treatment group, 15 PMIs were prevented. However, this was achieved at an unacceptable expense of eight additional deaths and five strokes. Post hoc multivariate analysis pointed to significant hypotension as the largest population-attributable risk for death. Additionally, hypotension had a strong association with postoperative stroke. The numbers needed to harm were 130 and 190 for all-cause mortality and stroke, respectively.\textsuperscript{42} POISE exposed risks that were not revealed by the preceding smaller trials, and this illustrates the critical importance of conducting trials of sufficient statistical power to allow assessment of relatively uncommon but important outcomes.

In essence, the POISE protocol achieves an unfavourable balance between efficacy and safety. The findings underline the dilemma that clinicians currently face. Perioperative beta blocker therapy, as administered in POISE, is effective at reducing
perioperative myocardial ischaemia and its sequelae. However, the safety of the practice remains in question. The benefits cannot be safely achieved if the POISE protocol is followed.

Despite the fact that the largest randomised controlled trial in the field did not find overall favour for the practice,\(^4\) researchers and clinicians have found some encouragement in the results. It may be possible to balance efficacy and safety more favourably and, as a result, the focus has shifted to finding ways that may optimise the intervention. How best to initiate and titrate beta blockade has become a key consideration.\(^{43}\)

Experts have suggested that the dose of metoprolol used in POISE was too high.\(^{44}\) The POISE protocol allowed for up to 100% of the maximum recommended therapeutic daily dose (MRTD) of metoprolol to be administered to beta blocker-naïve patients on the day of major surgery.\(^{45}\) In contrast, lower doses (10–20% MRTD) of bisoprolol, titrated over a minimum of seven days, seems to be a safer strategy.\(^{45,46}\) The incidence of stroke in the DECREASE trials was not significantly increased (OR 1.16, 95% CI 0.4–3.4),\(^{45}\) unlike the increased risk demonstrated in the POISE trial (OR 2.2, 95% CI 1.3–3.8).\(^8\)

Titration may also increase efficacy. A longer lead in period could allow tighter heart rate control with a lesser risk of clinically significant bradycardia and hypotension.\(^{46,47}\) Effective control of heart rate may be a critical determinant of cardioprotection.\(^{25,26}\) However, even this remains controversial.\(^{49,50}\) In addition, potentially important anti-inflammatory and plaque stabilising effects of beta blockers may take several days to develop.\(^{21}\)

**Conclusions drawn from inconclusive evidence**

The literature remains inconsistent and confusing as a result of fundamental differences in study design. Few reliable conclusions can be drawn from the currently available data. The marked heterogeneity and insufficient power of the small number of randomised trials make comparisons difficult, if not inappropriate.

Attempts at clarifying best practice have received priority in the post-POISE era. Multiple reviews,\(^{47,51-53}\) commentaries,\(^{44,54}\) and an editorial,\(^{42}\) with suggested recommendations for perioperative beta blockade, have been published. The European Society of Cardiologists (ESC) has published guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery.\(^4\) In addition, the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) were compelled to update their 2007 consensus guidelines with respect to perioperative beta blockade.\(^{22}\) The confusion is best illustrated by the differences in recommendations for perioperative beta blockade between these sources of expert review.

The same body of literature was available for interpretation, and yet expert consensus guidelines on opposite sides of the Atlantic differ.\(^{4,22}\) The Europeans, under the chairmanship of Poldermans, derive at least some of their recommendations from underpowered trials conducted within Europe.\(^{31,55-57}\) Both groups consider the POISE findings, but the ACCF/AHA have recommended a more conservative and restricted approach.\(^{22}\) Concentrating on similarities rather than differences, however, may select more robust recommendations that promote an acceptable balance between efficacy and safety. A diagram (Figure 1) has been created to illustrate an approach that concentrates on common themes expressed in consensus guidelines and recent reviews.

Firstly, there is consistency in recommending the continuation of beta blockers in patients with an appropriate indication for their use.\(^{4,22,42-44,47,51-54}\) Withdrawal of beta blockade in the perioperative period is associated with an adverse effect on outcome.\(^{25,26}\) Secondly, the need to titrate beta blocker therapy to heart rate and blood pressure is a further area of agreement.\(^{4,22}\) The guidelines differ slightly in the recommended targets of titration, and the period over which this titration should occur. Further investigation is essential, as the proposed benefits of titration are not proven and rely on limited data.\(^{31,57}\) Interventions requiring a regular reassessment of patients may create significant logistical problems. Feasibility may be limited in resource constrained environments. It remains unclear whether the potential benefits of titration relate to efficacy or safety. If related to efficacy, then a prolonged titration phase may be necessary to allow time for all beneficial effects. If related to safety only, provided due attention is paid to potential adverse effects, it seems feasible that titration could be achieved over a much shorter interval. (These two recommendations are indicated by blue text in Figure 1. Exit from the narrow end of the funnel at the bottom of the diagram corresponds to recommendations for the use of beta blockers.)

There is also a degree of consistency regarding practices that are not recommended. Both guidelines specifically do not recommend high dose beta blockers without titration in the perioperative setting.\(^ {4,22}\) Further agreement includes the avoidance of beta blockers.
in patients who have a contraindication to their use. (Red text is used in Figure 1 to emphasise these two practices that are not recommended. They are positioned to the right side of the funnel.)

It is important to be aware that any further recommendations rely on interpretation of inconclusive evidence from a body of literature riddled with inconsistencies. For all other groups of patients, the risks and benefits of perioperative beta blockade should be evaluated on an individual basis.

High risk patients, undergoing high risk procedures, are more likely to benefit from beta blockers than patients with intermediate or lower overall risk. Patients at the highest risk are those with known ischaemic heart disease (IHD) or myocardial ischaemia on preoperative testing, and patients undergoing high risk surgery with multiple clinical risk factors (CRFs). The ESC guidelines award a Class 1 recommendation for beta blockers in these groups of patients. The POISE data cannot, however, be interpreted as supportive evidence for these recommendations.
Although not reaching statistical significance, it is perhaps noteworthy that patients undergoing vascular surgery showed a beneficial reduction in the primary endpoint on subgroup analysis of the POISE data. In Figure 1, the above two categories are represented by green text and are situated closest to the exit of the funnel. Groups of patients depicted closest to the exit of the funnel warrant a low threshold for introduction of beta blockers pre-operatively. If introduced, the beta blocker medication should be titrated.

The lower the risk classification of the patient or the procedure, the lower the potential becomes for significant benefit. The point at which the risk outweighs the potential benefit remains unknown. There is some evidence in favour of beta blockade in patients of intermediate risk. However, these studies are not adequately powered to assess important adverse events. A study by Biccard et al showed possible benefit in patients of intermediate risk undergoing vascular surgery, but a reduced potential for benefit in those of intermediate risk undergoing intermediate risk surgery. It is reasonable to consider perioperative beta blockade in patients at intermediate risk undergoing vascular surgery, and in patients with multiple clinical risk factors undergoing intermediate risk surgery. However, it is important to note that this is a consideration rather than a recommendation, and requires an individualised approach. (These two groups are illustrated in bold black text within the funnel in Figure 1.)

Patients at lower risk, with fewer clinical risk factors, may be harmed by the introduction of perioperative beta blockade. It seems prudent that these patients should not be subjected to the potential risks until further favourable evidence is obtained. (In Figure 1, groups of lower risk patients fall outside of the funnel towards the right side of the diagram, and are highlighted in orange.)

There is insufficient evidence to guide decision making in the remaining patient groups. Interventions should be individualised, but caution is advised. (In Figure 1, these groups are allocated fine black text and hover above the funnel.)

Opinions and recommendations

The complications associated with high risk patients undergoing major non-cardiac surgery present an increasing burden on health systems. Strategies to reduce these complications must remain a research priority.

The management of tachycardia in the perioperative setting should always be directed at potential underlying causes, before beta blockers are considered. Anaemia and hypothermia are associated with adverse perioperative cardiac events in patients at risk, and must be prevented. Pain, hypovolaemia and infection are further causes of increased myocardial oxygen demand that need to be addressed.

The use of statins is recommended in patients at significant risk for adverse cardiac events. There is growing evidence for the beneficial pleiotropic effects of these agents.

Chronic beta blockade should be continued throughout the perioperative period.

A pro-active approach is recommended in patients at the highest risk for adverse cardiac events. The use of clinical discretion is encouraged. Individualised management is particularly important in patients at intermediate risk of adverse events.

Further testing should be considered but only in situations where it would change management. Test results may support a delay in surgery to allow optimisation of medical therapy in high risk patients. In addition to beta blockers, this may include statins, ACE inhibitors and aspirin. The results of preoperative testing may also allow for more accurate counseling of high risk patients, and could be used to aid in the process of recommending a less invasive intervention. It is uncommon practice to use results of preoperative testing to determine suitability for preoperative coronary revascularisation in asymptomatic patients, as results of this practice have not shown increased benefit.

Titration of beta blockade is recommended. The limited evidence precludes a firm recommendation regarding targets of titration. It is reasonable to titrate to a heart rate between 60 and 80 beats per minute, and to maintain blood pressure within 20% of the patient’s baseline in an attempt to remain within a zone of potentially retained optimal autoregulatory function. This is one of the most important areas requiring further research.

Post-POISE, greater emphasis must be placed on the monitoring of patients. There is no instructive evidence from previous studies. It is plausible that effective monitoring does not necessarily require a more invasive approach. More regular assessment of simple measures of haemodynamic status, such as noninvasive blood pressure and heart rate, are recommended. When combined with a greater level of awareness of the potential for adverse events, these
measures may be sufficient to optimise safety, both pre- and postoperatively.

Conclusion

The optimal approach to risk reduction remains elusive. Perioperative beta blockade is not a benign intervention, and evidence for the overall benefit of the practice is inconclusive. However, unless alternative effective and safe strategies are found to modify risk, beta blockers must be considered as an optional intervention in patients at high risk for perioperative cardiovascular events.

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