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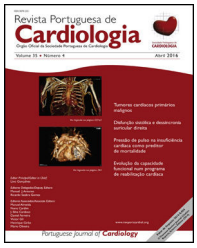

EDITORIAL COMMENT

Beta-blockers: Protective against perioperative stress, but not for all – as the evidence shows

Betabloqueantes, protetores de *stress* perioratório, mas não para todos... a evidência comprova

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Any type of surgery will cause body stress and may lead to negative clinical outcomes, including myocardial ischemia or infarction, arrhythmias, heart failure, stroke and, in some cases, death. This response is aggravated by any pre-existing cardiac morbidities, such as coronary artery disease or heart failure.

Beta-blockers are well known for attenuating the stress response, mainly by slowing heart rate and lowering blood pressure. Over the last two decades a number of studies have investigated the use of beta-blockers in patients who are subject to severe surgical stress and are at significant risk of major adverse cardiac events (MACE) and death, in the context of both cardiac and non-cardiac surgery. While the effects of beta-blockers are desirable to fight the stress response, the same effects – if too marked – may cause very low blood pressure and a very low pulse, eventually leading to MACE.

The paper by Alegria et al. in this issue of the *Journal*[1] assesses the Cochrane systematic review by Blessberger et al. on perioperative beta-blockers for preventing surgery-related mortality and morbidity.[2] The review analyzes 88 randomized controlled clinical trials (53 involving cardiac surgery and 35 non-cardiac surgery) including 19 161 participants in terms of MACE and other outcomes following surgery.

The review found no evidence of any effect of beta-blockers on patients undergoing cardiac surgery regarding all-cause mortality, acute myocardial infarction, myocardial ischemia, stroke, hypotension, bradycardia or heart failure, but found a beneficial effect in reducing ventricular arrhythmias and supraventricular arrhythmia, possibly leading to a slight reduction in hospital stay.

Regarding non-cardiac surgery, the review found that beta-blockers increased the risk of hypotension and bradycardia and possibly also of all-cause mortality and stroke.

It seems clear that the endpoints of myocardial ischemia, infarction and supraventricular arrhythmias are reduced by the use of beta-blockers, while the endpoints of ventricular arrhythmias, heart failure and length of stay are largely unaffected.

Theoretically, these well-demonstrated favorable effects of beta-blockers on myocardial ischemia and arrhythmias should protect both cardiac and non-cardiac surgical patients. However, these protective effects were offset by a potential increase in mortality and stroke seen in the non-cardiac surgery group, while their use was favorable for

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cardiac surgical patients, for whom it improved their clinical outcomes.

While medicine should rely more and more on evidence – of the type that is generated mainly by large randomized trials, such as those so thoroughly reviewed by Cochrane, and that this paper echoes – one must be cautious due to the nature of these trials, since they in fact analyze a case mix. On the basis of this analysis, they develop general rules that physicians are supposed to apply to individual cases and to particular patients. Let me specify:

(1) Beta-blockers are competitive antagonists that block the receptor sites for the endogenous catecholamines epinephrine and norepinephrine on adrenergic beta receptors of the sympathetic nervous system, which mediates the fight-or-flight response. Some will block activation of all three known types of beta-adrenergic receptors, while others are selective for one of the three organ-specific types. Beta-blockers all differ in terms of power and action. Furthermore, drug dosages and treatment duration are important, particularly if the patient was on chronic beta-blocker therapy prior to surgery, as opposed to starting the drug the day before. It is also relevant that in some cases, beta-blocker dosage should be adjusted just prior to surgery, which may reduce any possible negative drug-related action.

All these variables are flattened in the present analysis, by the number of cases and the case mix, although it is uncertain to what extent this affects the final conclusions.

(2). Not all patients are the same. Cardiac surgery patients, in whom beta-blockers appear to have a beneficial effect, have a cardiac lesion that is to be corrected by surgery, while non-cardiac patients may be healthy in cardiac terms, or they have some cardiac comorbidity, such as hypertension, myocardial ischemia or infarction, or heart failure, or suffer from silent cerebrovascular disease. The latter patients will tolerate the hypotensive effects of beta-blockers less well, and thus see their stroke and mortality risk worsen, as demonstrated in the Cochrane analysis. So separating the analysis into cardiac versus non-cardiac surgery is in fact a gross simplification, as the characteristics of these two patient groups are very different. As an example, a recent paper by Park et al.[3] addressed non-cardiac surgery patients, with successful myocardial revascularization and without systolic dysfunction, and concluded that for these patients, the use of perioperative beta-blockers was not associated with any negative clinical outcomes.

Once more, analysis of a case mix will flatten the unbalanced nature of cohorts, in a way that can distort the real tendencies. Some trials are less robust than others in terms of the evidence generated, possibly due to the uneven nature of patient populations.

(3) Finally, the types of surgery are different. Cardiac surgery patients may be undergoing coronary or valvular procedures, which have different potential for associated ischemia and arrhythmias, and will therefore respond differently to beta-blockers, while non-cardiac surgery patients undergo operations that may be more or less stressful, with more or less blood loss and alterations in blood pressure. Again, these are all flattened in the case mix, and this may also compromise the results of the analysis.

We are living in a time of evidence-based medicine, and we now practice according to guidelines. That is positive, but we must be careful when trying to apply these 'rules' to individual patients. In fact, analysis of a case mix dilutes most of the variation, but while this is true, its significance is threatened by the Pareto principle, which long ago established that 80% of any variation is determined by 20% of causes. This could easily cast doubt on the evidence for the negative effects of beta-blockers in non-cardiac surgical patients as an absolute indication, as they might in fact be extremely useful for the general population without myocardial ischemia, by reducing stress on the heart and circulation.

A good friend of mine, who recently passed away, used to allude to the advantages of 'evidence based on medicine' as opposed to 'evidence-based medicine'. What was meant was medicine that would take into account the general rule but be personal and personalized to a particular patient; in fact, anticipating what is now called 'precision medicine'. Such medicine, in line with the ideal combination of generalization plus particularization, should always be preserved. As for the mathematics, to quote Sir Berkeley Moynihan, ''statistics will prove anything, even the truth.''

I truly enjoyed reading this useful paper, I congratulate the authors and I strongly recommend it to the readers of the *Journal*.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Alegria S, Costa J, Carneiro AV, et al. Cochrane corner: perioperative beta-blockers for preventing surgery-related mortality and mortality. Rev Port Cardiol. 2020;38, http://dx.doi.org/10.1016/j.repc.2018.10.014. S0870-2551(19)30573-6. [Epub ahead of print].
2. Blessberger H, Kammler J, Domanovits H, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. Cochrane Database Syst Rev. 2018;3:CD004476.
3. Park J, Kim J, Kwon JH, et al. Association between perioperative β-blocker use and clinical outcome of non-cardiac surgery in coronary revascularized patients without severe ventricular dysfunction or heart failure. PLOS ONE. 2018;13:e0201311.