Does preoperative beta-blocker offer myocardial protection during coronary artery bypass grafting?

Betabloqueador pré-operatório confere cardioproteção em revascularização do miocárdio?

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The past two decades have seen a number of studies being carried out in order to investigate the use of beta-blockers as myocardial protection in patients who undergo great surgical stress and are under significant risk factors, especially in non-cardiovascular surgery regarding major adverse cardiac events (MACE) and death [1,2].

During meta-analysis published in 2010, which included the patient profile described above, Angeli et al. [3] showed that the use of beta-blockers did not have an impact on mortality (odds ratio [OR] 1.15; confidence interval [CI] of 0.92-1.43; *P* = 0.2717). Despite meta-analytical rigor, the heterogeneity of the clinical trials included in the study make it difficult to undertake a detailed analysis, mainly as a result of the large range of surgical procedures and risk factors. Stevens et al. [4] stated that the prophylactic use of beta-blockers in high risk patients who underwent major surgery showed, in a series of clinical trials, variation in the number needed to treat (NNT) ranging from 2.5 to 8.3; whereas studies with lower hierarchy showed NNT of 32 to reduce mortality.

That being said, the guidelines of both North American associations for cardiology, "Joint American College of Cardiology" and "American Heart Association", recommend the use of beta-blockers in patients with confirmed myocardial ischemia (Class I, LOE B) and in other high risk patients (class IIa, LOE B) undergoing non-cardiovascular surgery [5]. Note that the guidelines were published in 2007, before the 2008 POISE study, which included 8350 patients randomized to receive metoprolol succinate in the preoperative period and up to 30 days after non-cardiac surgery [6]. The results showed that 176 patients (4.2%) from the metoprolol group developed acute myocardial infarction (AMI) versus 239 (5.7%) from the control group; Hazard Ratio (HR) of 0.73 (0.60-0.89: *P*=0.0017). However, the metoprolol group had higher mortality and cerebral ischemia than the control group, 3.1% versus 2.3%; HR 1.33 (1.03-1.74: *P*=0.0317) and 1.0% versus 0.5%; HR 2.17 (1.26-3.74: *P*=0.0053), respectively. On the other hand, the use of beta-blockers for acute ST segment elevation myocardial infarction is well established (class I, LOE A). There is a scientific gap as far as myocardial protection offered by beta-blockers in patients who underwent cardiovascular surgery is concerned, especially in the surgical treatment of coronary disease.

SEE ORIGINAL ARTICLE ON PAGES 449-454

In the 1990s, Mair et al. [7] described the characteristics of Troponin I (TnI) and Troponin T distribution after myocardial lesions, peak plasma concentrations (up to 12 hours), and TnI specificity for cardiac muscle apoptosis. Antman et al. [8], in a multicenter study, evaluated TnI values in 1440 people with angina pectoris. Out of the 1440, 573 patients, with serum TnI levels above 0.4 ng/ml, had higher mortality in 42 days of follow-up. The study showed that, quantitatively, there is a strong correlation between higher serum TnI levels and death as the outcome. Subsequently, in Brazil, Leal et al. [9] analyzed serum TnI levels in patients who had undergone myocardial revascularization. In that study, the authors found there was correlation between the quantitative value of TnI measured by chemiluminescence whenever it was above 2.5 ng/ml on the first postoperative day and increased mortality in 30% to 50% in the first six months after surgery.

In the present issue, considering the assumptions set forth above, the authors describe a randomized clinical trial based on the following questions [10]:

1. Does the use of beta-blockers introduced 72 hours before coronary artery bypass grafting surgery alter serum TnI levels in the postoperative period?

1. Cirurgião Cardiovascular. Cirurgião Associado do MSF-Médicos Sem Fronteiras. Fellowship em CCV Pediátrica- Necker-França

2. Are there secondary changes to cardiovascular, morbidity, and mortality outcomes?

In order to answer the first question, despite the small sample size (68 patients), in terms of low incidence outcomes, the authors showed that, using the immunometric method, TnI concentrations were "…lower in group B than in group A (2.5 ng/ml versus 3.7 ng/ml, $P<0.05$)". Patients in Group B were administered 200 mg/day metoprolol tartrate in the preoperative period and Group A was the control. There was no statistically significant difference between the groups in terms of clinical outcomes (see Table 6 – page 452). There was also acute atrial fibrillation in three patients from Group A and one patient from Group B ($P=0.27$). In addition, average baseline heart rate was 73.8 bpm ± 1.7 in Group A, higher than the average in Group B, which was 68.0 bpm ± 1.7 ($P=0.021$). Thus, this variable was heterogeneously distributed between groups A and B, previous randomization notwithstanding. Multivariate analysis showed there was an increase in serum Troponin I levels at 12 hours postoperative in Group A (control) compared to Group B (metoprolol).

As far as the second question is concerned, the study lacked statistical power to determine differences in clinical outcomes, such as greater use of vasoactive drugs for longer than 24 hours by Group B (metoprolol) ($P=0.085$), likely constituting a type II error. Therefore, it is advisable not to make assumptions about the "prophylactic" use of metoprolol tartrate before CABG based on these results from clinical application. In short, subsequent studies in this interesting area can help determine the clinical impact of using beta-blockers as premedication in patients undergoing CABG and whether it is safe.

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