Myocardial protection with prophylactic oral metoprolol during coronary artery bypass grafting surgery: evaluation by troponin I

Proteção cardíaca com uso profilático de betabloqueador oral em cirurgia de revascularização miocárdica: avaliação pela troponina I

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Abstract

Introduction: Biochemical markers of myocardial injury are frequently altered after cardiac surgery. So far there is no evidence whether oral beta-blockers may reduce myocardial injury after coronary artery bypass grafting.

Objective: To determine if oral administration of prophylactic metoprolol reduces the release of cardiac troponin I in isolated coronary artery bypass grafting, not complicated by new Q waves.

Methods: A prospective randomized study, including 68 patients, divided in 2 groups: Group A (n=33, control) and B (n=35, beta-blockers). In group B, metoprolol tartrate was administered 200 mg/day. The myocardial injury was assessed by troponin I with 1 hour and 12 hours after coronary artery bypass grafting.

Results: No significant difference between groups regarding pre-surgical, surgical, complication in intensive care (15% versus 14%, P=0.92) and the total number of hospital events (21% versus 14%, P=0.45) was observed. The median value of troponin I with 12 hours in the study population was 3.3 ng/ml and was lower in group B than in group A (2.5 ng/ml versus 3.7 ng/ml, P<0.05). In the multivariate analysis, the variables that have shown to be independent predictors of troponin I release after 12 hours were: no beta-blockers administration and number of vessels treated.

Conclusion: The results of this study in uncomplicated coronary artery bypass grafting, comparing the postoperative release of troponin I at 12 hours between the control group and who used oral prophylactic metoprolol for at least 72 hours, allow to conclude that there was less myocardial injury in the betablocker group, giving some degree of myocardial protection.

Descriptors: Troponin I. Postoperative care. Adrenergic beta-antagonists.

Resumo

Introdução: Os marcadores bioquímicos de lesão miocárdica estão frequentemente alterados após cirurgia cardíaca. Até o momento não existem evidências de que o betabloqueador oral possa reduzir a lesão miocárdica após cirurgia de revascularização miocárdica.

Objetivo: Determinar se a administração oral profilática de metoprolol reduz a liberação de troponina cardíaca I na cirur-
INTRODUCTION

An increase in troponin levels is observed following cardiac surgery, indicating myocardial injury [1,2]. The values considered normal or expected after coronary artery bypass grafting (CABG) suffer multifactorial influences such as type of surgery, duration of ischemia and myocardial protection, inflammatory response, reperfusion injury, excessive stretching and contraction of the heart, atheromatous embolism, inadequate coronary perfusion and excessive perioperative cardiac work.

Beta-blockers can be defined as pharmacologic agents that antagonize specifically, competitive and reversible the action of endogenous or exogenous catecholamine in beta-adrenergic receptors. Particularly in the heart, beta-adrenergic stimulation leads to increased heart rate and myocardial contractility. Depending upon the selective ability to antagonize the effects of catecholamines in certain tissues at doses lower than those required in others, beta-blockers may be classified as selective and non-selective. The beta-1 selective blockers are considered cardiospecific because the heart contains predominantly beta-1 and less beta-2; since the bronchodilation is mediated by beta-2 receptors, and this characteristic is dose-dependent and decreases or disappears when employing high doses. Possible deleterious effects resulting from the use of beta-blockers that could cause myocardial depression and/or worsening of existing lung disease, however, are of concern for some cardiac surgeons.

The clinical benefits of beta-blocker therapy have been proven in the treatment of myocardial infarction, heart failure, protection of preoperative patients with ischemic heart disease and in the prevention of atrial fibrillation postoperatively [3,4].

From the clinical and research perspective, it is desirable to describe the plasma levels of markers of myocardial necrosis (MMN) as troponins, released in CABG that are not caused by infarction postoperatively and evaluate possible myocardial protection procedures that could reduce the MI. It is plausible to expect that the results of the protective effects of beta-blockers can be extrapolated to CABG. Therefore, the aim of this study is to test the hypothesis that the prophylactic use of oral metoprolol tartrate reduces MI, assessed by the release of troponin I (Tnl) in the first 12 hours of post-CABG alone and not complicated by the presence of new Q waves on the electrocardiogram (EKG), conferring myocardial protection.

METHODS

This is a randomized, open-label and single center study. Inclusion criteria for the study were indication for CABG regardless of age or gender with signed informed consent term. Exclusion criteria for the study were: previous use of beta-blockers; contraindication to beta-blockers; clinical signs of systolic heart failure, global ejection fraction less than 50%; CABG associated with other procedures (valve replacement or aneurysmectomy or endoaneurysmorrhaphy), presence of new Q waves on EKG during the period of stay in the Intensive Care Unit (ICU) and presence of acute myocardial infarction less than 30 days of evolution.

All patients underwent CABG with the same surgical technique (intermittent aortic clamping) and a graft of the left internal thoracic artery had to be implanted.

The metoprolol tartrate (oral) was initiated at least 72 hours before surgery, in the target dose of 200 mg/day.

Tnl concentrations were determined by immunometric method using the Immulite Analyser (DPC - Diagnostic Products Corporation - Los Angeles, USA). Three samples
of blood were collected for the determination of TnI: in the preoperative period, with one hour and 12 hour arrival in the ICU. A program developed by the authors of the EuroSCORE was used for the score calculation of each patient [5].

The intercurrences and complications (inotropes >24 hours, intubation >24 hours, temporary pacemaker, the ICU stay for >24 hours, stroke, atrial fibrillation, and death) were registered in the medical record and transferred to the clinical form of the study.

Due to the difficulty of finding information on the variability of the difference between TnI between the two groups (with and without beta-blockers) initially several simulations were performed to estimate the sample size. After the completion of the study, the statistical difference (1.2) and standard deviation of the difference (1.7) were calculated, and it was observed a test power of 85%.

Results were expressed as mean and standard error or median and quartiles for quantitative variables, while qualitative variables were expressed as relative frequencies. Possible associations between qualitative variables were evaluated using the chi-square or Fisher exact test. For comparison of quantitative variables between the control and beta-blocker groups was used t-test for variables with normal distribution and for those without normal distribution (with an hour I TnI, TnI 12 hours and number of vessels treated) the Mann-Whitney test was applied. The Spearman correlation was used to examine the association between quantitative variables and TnI of 12 hours.

For the choice of the independent variables on the model of multivariate analysis, variables that had significant correlation were selected and by clinical judgment the ones that could also influence the release of TnI 12 hours. For the selection of best model, which had a reduced number of variables the Akaike criterion and cross-validation were selected and by clinical judgment the ones that could also influence the release of TnI 12 hours. For the selection of best model, which had a reduced number of variables the Akaike criterion and cross-validation were selected and by clinical judgment the ones that could also influence the release of TnI 12 hours. For the selection of best model, which had a reduced number of variables the Akaike criterion and cross-validation were selected and by clinical judgment the ones that could also influence the release of TnI 12 hours.

The Spearman correlation was used to examine the association between quantitative variables and TnI of 12 hours.

Table 1. Qualitative variables, comparison of the control and beta-blocker groups.

| Variables                | Control N (%) | Beta-blocker N (%) | P-value |
|--------------------------|---------------|-------------------|---------|
| Female                   | 11 (33)       | 11 (31)           | 0.867   |
| Indication               |               |                   |         |
| - Stable angina          | 23 (70)       | 27 (80)           | 0.312   |
| - Unstable angina        | 04 (12)       | 01 (03)           |         |
| - Anatomic               | 02 (06)       | 04 (11)           |         |
| - Silent schema          | 04 (12)       | 02 (06)           |         |
| Prior infarction         | 12 (36)       | 16 (46)           | 0.434   |
| Prior revascularization  | 01 (03)       | 0                 | 0.299   |
| Transient ischemic attack| 0             | 02 (06)           | 0.163   |
| Diabetes mellitus        | 11 (33)       | 12 (34)           | 0.934   |
| Hypertension             | 25 (76)       | 25 (71)           | 0.686   |
| Dyslipidemia             | 18 (54)       | 25 (71)           | 0.149   |
| Current smoking          | 08 (24)       | 05 (14)           | 0.554   |
| Family history of CoI    | 05 (15)       | 08 (23)           | 0.419   |

N= number of patients; CoI = coronary insufficiency

Table 2. Quantitative variables, comparison of the control and beta-blocker groups.

| Variables          | Control Mean ± SE | Beta-blocker Mean ± SE | P-value |
|--------------------|-------------------|------------------------|---------|
| Age (years)        | 59.0 ± 1.7        | 57.9 ± 1.4             | 0.619   |
| Weight (Kg)        | 72.3 ± 3.0        | 74.8 ± 2.4             | 0.519   |
| Height (m)         | 1.63 ± 1.0        | 1.65 ± 1.0             | 0.330   |
| BMI (Kg/m²)        | 26.7 ± 0.8        | 27.1 ± 0.8             | 0.740   |
| Risk index – EUROSCORE | 0.21 ± 0.3     | 02.0 ± 0.3             | 0.757   |
| Ejection fraction  | 64.0 ± 1.0        | 66.3 ± 1.1             | 0.153   |
| Pre-operative heart rate | 73.8 ± 1.7     | 68.0 ± 1.7             | 0.021   |

SE= standard error; BMI= body mass index

Table 3. Surgical characteristics in the control and beta-blocker groups.

| Variables                | Control group Mean ± SE | Beta-blocker group Mean ± SE | P-value |
|--------------------------|-------------------------|------------------------------|---------|
| Perfusion time (minutes) | 86.8 ± 5.2              | 84.1 ± 5.1                  | 0.705   |
| Cross clamp time (minutes)| 60.3 ± 3.0             | 57.0 ± 3.6                  | 0.477   |
| ICU stay (hours)         | 45.4 ± 1.4              | 54.3 ± 6.2                  | 0.181   |
| Number of grafts performed | 3.0 (2.0-3.0)    | 3.0 (2.0-3.0)               | 0.215   |

Table 4. Analysis of troponin I results (ng/ml) in both groups.

| Troponin I | Control Group Median (25%-75%) | Beta-blocker Group Median (25%-75%) | P-value |
|------------|--------------------------------|-------------------------------------|---------|
| Pre-operative | 0.5 (0.5-0.5)              | 0.5 (0.5-0.5)                      | 0.303   |
| At 1 hour   | 2.7 (1.2-5.0)               | 2.1 (1.0-4.2)                      | 0.360   |
| At 12 hours | 3.7 (2.2-9.9)               | 2.5 (1.9-4.9)                      | 0.048   |

RESULTS

Initially 70 patients were selected and after recruitment, two cases were not considered from the analysis because they had new Q waves on EKG 12 hours after surgery.

Patients were allocated for two groups, 33 (48.5%) patients in the control group, and the other 35 (51.5%) in the beta-blocker group. The dose in one patient was reduced to 100 mg/day due to asymptomatic heart rate less than 50 bpm.

The clinical and surgical characteristics of the groups are described in Tables 1, 2 and 3.

Table 4 presents the results of the values of Tn I with 1 hour and 12 hours of arrival in the ICU between the control and beta-blockers. Tn I values were lower in the beta-blocker group than in the control group.
However, this difference was only statistically significant in the 12 hours postoperatively data (2.50 versus 3.70, P=0.048).

The changes of TnI were analyzed 12 hours post-operative and their association with some clinical and surgical variables. In addition to the variable group, univariate analysis showed that the factors to be correlated with the release of TnI 12 hours were perfusion time, cross clamp time and the number of grafts performed (Table 5). Although statistically significant, this relationship was considered weak by analyzing the values of correlation (R).

### Table 5. Correlation between troponin I at 12 hours of postoperative and variables which could influence its release.

| Variable                  | Correlation (R) | P-value |
|---------------------------|-----------------|---------|
| Weight                    | -0.10           | 0.379   |
| Height                    | 0.02            | 0.886   |
| BMI (body mass index)     | -0.17           | 0.160   |
| Age                       | 0.06            | 0.622   |
| Ejection fraction         | -0.10           | 0.557   |
| Preoperative heart rate   | 0.11            | 0.466   |
| Perfusion time            | 0.30            | 0.016   |
| Cross clamp time          | 0.30            | 0.011   |
| Number of grafts performed| 0.36            | 0.003   |

There was no significant difference in relation to postoperative complications in the ICU and in-hospital events between groups (21% in the control group versus 14% in patients with beta-blocker, P=0.454) (Table 6).

In the final model of the multivariate analysis, the variables that have shown to be independent predictors of TnI release after 12 hours were: no beta-blockers administration and number of grafts required. Table 7 shows the percentage increase and the results expected. No beta-blockers administration increases in 22% the expected value of troponin 12 hours and for each graft required adds a 33% increase.

### DISCUSSION

The results of this study prospectively evaluated 68 patients undergoing isolated CABG revealed for the first time in literature, a myocardial injury reduction in the group using oral beta-blocker at a dose of 200 mg/day for at least 72 hours preoperatively.

Some demographic characteristics in the general population of the study should be highlighted as the presence of women in one third of patients, average age below 60 years, more than a third with previous myocardial infarction, diabetes.

### Table 6. Comparison of complications in the intensive care unit and hospital events between the control and beta-blocker groups.

| Variables                                | Control Group n (%) | Beta-blocker Group n (%) | P-value |
|------------------------------------------|---------------------|--------------------------|---------|
| Complications in the ICU                 |                     |                          |         |
| - Inotropic agents > 24 hours            | 0                   | 03 (09)                  | 0.085   |
| - Temporary pacemaker                    | 01 (03)             | 0                        | 0.299   |
| - Intubation > 48 hours                  | 01 (03)             | 03 (09)                  | 0.332   |
| - ICU > 48 hours                         | 04 (12)             | 05 (14)                  | 0.792   |
| - Stroke                                 | 01 (03)             | 01 (03)                  | 0.966   |
| - Atrial fibrillation                    | 03 (09)             | 01 (03)                  | 0.275   |
| - ICU deaths                             | 00                  | 01 (03)                  | 0.328   |
| - Total complications in the ICU         | 06 (18)             | 05 (14)                  | 0.457   |
| Hospital events                          |                     |                          |         |
| - Hospital deaths                        | 01 (03)             | 01 (03)                  | 0.966   |
| - Total hospital events                  | 07 (21)             | 05 (14)                  | 0.454   |

n = number of patients; ICU = Intensive Care Unit.

### Table 7. Results of the multivariate analysis of troponin I release at 12 hours.

| Variables                          | Expected Percentage Increase | CI 95%       | P-value |
|------------------------------------|------------------------------|--------------|---------|
| Control group                      | 1.22                         | 1.02-1.46    | 0.027   |
| Number of grafts performed         | 1.33                         | 1.01-1.77    | 0.046   |
| Hospital events                    | 1.65                         | 0.97-2.80    | 0.063   |
| Perfusion time                     | 1.00                         | 0.99-1.01    | 0.077   |
| Postoperative complications        | 0.64                         | 0.36-1.14    | 0.132   |
for at least 72 hours, allow us to conclude that there was less myocardial injury in the beta-blocker group, conferring myocardial protection.

| Author’s roles & responsibilities |
|-----------------------------------|
| JMRN | Protocol design, data collection, discussion of results and manuscript writing |
| CG   | Discussion of results |
| RFR  | Discussion of results |
| AFSA | Surgical procedures and discussion of results |
| MI   | Surgical procedures and discussion of results |
| VLA  | Data collection and discussion of results |
| JJD  | Discussion of results |
| LSP  | Protocol design, discussion of results and manuscript writing |

REFERENCES

1. Leal JCF, Braile DM, Godoy MF, Purini Neto J, Paula Neto A, Ramin SL, et al. Early evaluation of cardiac troponin I in patients submitted to myocardial revascularization. Rev Bras Cir Cardiovasc. 1999;14(3):247-53.

2. Califf RM, Abdelmeguid AE, Kuntz RE, Popma JJ, Davidson CJ, Cohen EA, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol. 1998;31(2):241-51.

3. Ong HT. Beta blockers in hypertension and cardiovascular disease. BMJ. 2007;334(7600):946-9.

4. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2011;141(5):1305-12.

5. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J. 2003;24(9):881-2.

6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60(16):1581-98.

7. Lurati Buse GA, Koller MT, Grapow M, Bolliger D, Seeberger M, Filipovic M. The prognostic value of troponin release after adult cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg. 2010;37(2):399-406.

8. Domanski MJ, Mahaffey K, Hasselblad V, Brenner SJ, Smith PK, Hillis G, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA. 2011;305(6):585-91.

9. Usta E, Mustafi M, Straub A, Ziemer G. The nonselective beta-blocker carvedilol suppresses apoptosis in human cardiac tissue: a pilot study. Heart Surg Forum. 2010;13(4):E218-22.

10. Fannelop T, Dahle GO, Matre K, Moen CA, Mongstad A, Eliassen F, et al. Esmolol before 80 min of cardiac arrest with oxygenated cold blood cardioplegia alleviates systolic dysfunction. An experimental study in pigs. Eur J Cardiothorac Surg. 2008;33(1):9-17.

11. Geissler HJ. Reduction of myocardial reperfusion injury by high-dose beta-blockade with esmolol. Thorac Cardiovasc Surg. 2002;50(6):367-72.

12. Booth JV, Landolfò KP, Chesnut LC, Bennett-Guerrero E, Gerhardt MA, Atwell DM, et al. Acute depression of myocardial beta-adrenergic receptor signaling during cardiopulmonary bypass: impairment of the adenylyl cyclase moiety. Duke Heart Center Perioperative Desensitization Group. Anesthesiology. 1998;89(3):602-11.

13. Taniguchi FP, Pego-Fernandes PM, Jatene FB, Kwasnicka KL, Strumz CMC, Oliveira SA. Implicação prognóstica da creatinoquinase miocárdica e troponina na revascularização do miocárdio. Rev Bras Cir Cardiovasc. 2003;18(3):210-6.