Rev Bras Cir Cardiovasc 2013;28(4):449-54

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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DOI: 10.5935/1678-9741.20130074

RBCCV 44205-1496

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-**

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No financial support.

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Article received on March 4th, 2013
Article accepted on July 10th, 2013

Abbreviations, acronyms & symbols	
CABG	Coronary artery bypass grafting
EKG	Electrocardiogram
ICU	Intensive Care Unit
MMN	Markers of myocardial necrosis
TnI	Troponin I

gia de revascularização miocárdica isolada não complicada por novas ondas Q.

Métodos: **Estudo prospectivo, randomizado, incluindo 68 pacientes divididos em 2 grupos: Grupo A (n=33, controle) e B (n=35, betabloqueador). No grupo B, o tartarato de metoprolol foi administrado na dose de 200 mg/dia. A lesão miocárdica foi avaliada pela troponina I com 1 hora e 12 horas após a cirurgia de revascularização miocárdica.**

Resultados: **Não foi observada diferença significativa entre os grupos quanto às variáveis pré-cirúrgicas, cirúrgicas, incidência de complicações na terapia intensiva (15% *versus* 14%; *P*=0,92) e o número total de eventos hospitalares (21% *versus* 14%; *P*=0,45). O valor da mediana da troponina I com 12 horas na população estudada foi de 3,3 ng/ml e foi menor no grupo B do que no grupo A (2,5 ng/ml *versus* 3,7 ng/ml; *P*<0,05). Na análise multivariada, as variáveis que demonstraram serem preditoras independentes da liberação de troponina cardíaca I com 12 horas foram: não uso de betabloqueadores e número de vasos tratados.**

Conclusão: **Os resultados desta investigação na cirurgia de revascularização miocárdica isolada, não complicada, comparando a liberação pós-operatória de troponina cardíaca I com 12 horas entre os grupos controle e o que usou metoprolol oral profilático por pelo menos 72 horas, permitem concluir que houve menor lesão miocárdica no grupo betabloqueador, conferindo algum grau de proteção miocárdica.**

Descritores: **Troponina I. Cuidados pós-operatórios. Antagonistas adrenérgicos beta.**

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 cardioselective 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 (TnI) 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.

TnI 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 Tn I 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 method was applied, that uses a generalized linear model of gamma distribution (link function log). The gamma model was selected by presenting a better fit in the residual analysis.

Results were considered statistically significant when *P*-values were less than 0.05.

This study was approved by the Ethics Research Committee of our Institution (protocol number: 2089).

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. TnI values were lower in the beta-blocker group than in the control group.

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 schemia	04 (12)	02 (06)	
Prior infarction	12 (36)	16 (46)	0.434
Prior revascularization	01 (03)	0	0.299
Transient schemic 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/m^2)	26.7 ± 0.8	27.1 ± 0.8	0.740
Risk index – EUROSCORE	02.1 ± 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

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.

	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

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