Trimetazidine and Inflammatory Response in Coronary Artery Bypass Grafting

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Abstract

Background: Organic inflammatory response is a pathophysiological mechanism present at every coronary artery bypass grafting with extracorporeal circulation (CABG-ECC), the release of inflammatory mediators being one of its defense mechanisms.

Objective: To assess, in a prospective double-blind randomized and placebo-controlled study, the effects of trimetazidine (Tmz) on the inflammatory response, by using the variation in interleukins 6 and 8, TNF-α, complements C3 and C5, and highly sensitive C-reactive protein (HS-CRP) levels in the pre- and post-operative periods.

Methods: This study assessed 30 patients undergoing CABG-ECC with intermittent hypothermic cardioplegia, and having, at most, mild ventricular dysfunction. The patients were divided into two groups (placebo and Tmz), stratified by echocardiography, and received drug/placebo at the dose of 60 mg/day. Measurements were taken as follows: in the pre-operative period with no drug; on the day of surgery, corresponding to 12 to 15 days on drug/placebo; five minutes after aortic unclamping; 12 and 24 hours after surgery, for interleukins and complements; and 48 hours after surgery, for HS-CRP.

Results: No significant difference between the levels of interleukin 8, TNF-α, C3 and C5, and HS-CRP was observed. However, the interleukin 6 levels were significantly lower in the group treated as compared with those in the control group at all time points assessed.

Conclusion: Trimetazidine proved to be effective only for reducing interleukin 6 in patients undergoing CABG. (Arq Bras Cardiol 2012;99(2):688-696)

Keywords: Trimetazidine/administration & dosage; inflammation; myocardial revascularization; myocardial reperfusion.

Introduction

The systemic inflammatory response present at all cardiovascular surgeries has become more evident since the development of the Extracorporeal Circulation (ECC) system by Jonh Gibbon in the 1950's, because it increases the blood exposure to an artificial system[1].

That activity, mediated by immune and cell response, can be analyzed by activating the complement system, thrombin, cytokines, neutrophils, adhesion molecules (Icam), mast cells, and other mediators[2].

Since the use of ECC, reperfusion – a pathophysiological phenomenon that intensifies the inflammatory response and can occur in coronary syndromes in general, in thrombolysis, and in angioplasty – has begun to represent the organic inflammatory changes related to coronary artery bypass grafting (CABG) after the release of the aortic clamp[3,4].

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The pathophysiology of reperfusion and its relation with inflammatory response has gained the attention of researchers because of its evident and important repercussions on the clinical cardiological practice, and has led to a better understanding of the events related. In particular, of the superoxide radicals, which are formed in the obstructions to coronary flow and can cause injury after aortic unclamping during heart surgery. Those superoxide radicals comprise the superoxide anion (O^{2}-), hydroxyl radical (OH), and hydrogen peroxide ($H^{2}O^{2}$), which can be removed from the cells by enzyme systems with antioxidant functions, usually present in myocardial physiology[5,6].

The superoxide radicals together with neutrophils act actively in the reperfusion injury, interacting in several sites and with other elements of the inflammatory cascade. During that aggression, platelets and leukocytes act via mediators (C3a, C5a, IL6, IL8, TNF-α, iNOS and superoxide radicals), causing direct damage to the myocardium[7,8].

Trimetazidine, with its anti-ischemic action, reduces the metabolic damage caused during ischemia by acting on a critical step of cardiac metabolism, blocking beta-oxidation of fatty acids by inhibiting the long-chain 3-acetyl-CoA thiolase. That anti-ischemic effect increases glucose oxidation,

additional to glycolysis, with the consequent reduction in protons, elevation of the intracellular pH and tissue acidosis, recovery of the cardiac efficiency, and improvement in the production of acetyl-CoA. In addition, it limits calcium build-up, inflammation and the production of superoxide free radicals that occur after reperfusion, without causing hemodynamic changes[6].

This study assessed the effects of Tmz on the inflammatory response triggered by CABG-ECC, performed with intermittent cold-blood cardioplegia, aiming at analyzing the myocardial reperfusion mechanisms, based on the variation of the plasma levels of IL6, IL8, TNF-α, C3, and C5, and on the assessment of highly sensitive C-reactive protein (HS-CRP), an acute-phase protein of the inflammatory response. In addition, the evolution of those post-operative mediators was also assessed.

Methods

This was a prospective, double-blind, randomized and placebo-controlled clinical trial, performed from July 2007 to August 2008 at the Instituto Estadual de Cardiologia Aloysio de Castro, state of Rio de Janeiro (Iecac-RJ). Its major objective was to examine the changes in the serum markers of inflammatory response of patients undergoing CABG-ECC with intermittent cold-blood cardioplegia, divided into two groups, one receiving Tmz and the other, placebo.

Martins et al.[6] have assessed 137 patients with echocardiographic indication for CABG-ECC, 75 of whom, with normal ventricular function or mild dysfunction, were selected. Of those, 60 patients, distributed in the treated and placebo groups, completed the tests for the serum markers of myocardial injury (troponin-T and CPK-MB). For the present study, 15 patients of each group were randomly selected, by using the Cytools Excel add-in software, for measuring the following inflammatory markers: IL6, IL8, TNF-α, C3, C5, and HS-CRP.

The samples of the 60 patients were collected in 5-mL Eppendorf tubes, forming four numerically arranged serum sets. Each of the participating centers (Laboratório Dasa – Diagnósticos da América, and Brownstein) received two of those sets simultaneously. The list of the patients selected was electronically sent.

Laboratório Dasa measured interleukins (IL6, IL8, and TNF-α) from the serum sets collected at the time points specified in the research protocol as follows: in the pre-operative period, in the presence of no drug; five minutes after aortic unclamping, directly from the right atrium; and 12 and 24 hours after surgery, from a deep catheter. The serum sets were kept at -70ºC and analyzed by use of flow cytometry (BD FACSCanto II™ flow cytometer).

Laboratório Brownstein measured C3 and C5, after storing at 4ºC the serum sets collected at the time points specified in the research protocol; C3 was analyzed by use of nephelometry (Dade Behring BN2 nephelometer), and C5, by radial immunodiffusion (Olympus AXl).

The HS-CRP tests were performed at Iecac-RJ by using nephelometry (Olympus AU400) at the time points specified in the research protocol: in the pre-operative period, in the presence of no drug; and 48 hours after surgery. Levels over 5mg/L were considered indicative of inflammation.

Trimetazidine was provided to patients after masking with randomization at the 1:1 proportion, permuted in blocks by the Cytools Excel add-in software. The examiners did not know which patients used drug or placebo. The statistical analysis was also conducted in a blind way, and the codes referring to drug/placebo were broken only after that.

The patients received 60 mg/day of drug/placebo divided into three daily doses, initiated 12-15 days prior to surgery. All 30 patients kept the drug for five to eight days after surgery, in a total of 20 days of drug/placebo use.

Patients underwent elective surgery according to a technique involving median sternotomy, and introduction of cannulae into the aorta and of one single cannula into the vena cava, in this sequence. Extracorporeal circulation was performed with moderate central hypothermia (32ºC-34ºC), and myocardial protection was provided by intermittent cold-blood cardioplegia (4ºC), infused in the aortic root or directly in the coronary sinus. All patients underwent balanced general anesthesia, venous-inhaling closed circuit, with CO_2 absorber and mechanical ventilation. Isoflurane with 50% oxygen, mixed with nitrous oxide, was used as inhaling agent. Regarding venous drugs, the following were used: as hypnotic agents, etomidate and midazolam; as opioid, fentanyl; and, as muscle relaxant, pancuronium bromide.

The significance level adopted was 5%. The statistical analysis used the 6.04 SAS software (SAS Institute, Inc., Cary, NC) and the following tests: Student *t* test or Mann-Whitney test for comparing numerical variables between the two groups; chi-square (α^2) test or Fisher exact test for comparing categorical variables between the two groups. For assessing the behavior of the variables over time according to the group of treatment, repeated measures analysis of variance (ANOVA) was used. Bonferroni adjustment for multiple comparisons was used to identify the time points that differed between themselves and between the groups. The variation between two CRP measurements at different time points was assessed by using the Wilcoxon signed rank test, and the corresponding variation (delta) was compared between the groups by using the Mann-Whitney test.

This study was approved by the Committee of Ethics in Research of the Iecac-RJ. Participants provided written informed consent and were followed up until hospital discharge.

The drug and the research material were provided by the major author. Randomization, masking, and software use were coordinated by a certified pharmacist, and donated by Farmacopa Ltda.

Results

Sample profile

Table 1 shows the general profile of the 30 patients selected for analysis, comparing the Tmz and placebo groups, and evidencing its homogeneity.

Table 2 shows the analysis of the surgical variables, which evidences uniformity of the Tmz and placebo groups regarding

the surgical procedures and the intensive care unit (ICU) length of stay.

Table 3 shows the descriptive analysis of the patients selected and non-selected who were treated with Tmz. Note the homogeneity of the groups regarding the surgical variables analyzed.

Analysis of the inflammatory markers

The analysis of the inflammatory markers showed that IL6 levels (Graphic 1) were significantly lower in the Tmz group as compared with those in the placebo group ($p = 0.012$). The same was not observed for the markers C3, C5, IL8, TNF-α and CRP (Graphics 2, 3, 4 and 5).

Discussion

The inflammatory response is always present in all cardiovascular surgeries, being more exuberant when ECC is used. Criteria precisely identifying the severity of the inflammatory response during and after cardiovascular surgery have been proposed, and several cutoff points for the biomarkers and therapeutic strategies have been proposed to reduce that response in clinical trials.

The 30 patients with two-vessel and three-vessel disease and normal or slightly impaired ventricular function were assessed by analyzing the inflammatory mediators C3, C5, IL6, IL8, and TNF-α, and HS-CRP in a prospective protocol that aimed at assessing the effects of Tmz in reducing those markers after reperfusion in CABG. The Tmz dose recommended was 60mg/day of the active substance, for at least 12 days before surgery, according to the bioavailability mechanism.

Transthoracic echocardiography was used to select only patients with normal or slightly impaired ventricular function by use of a segmentary contraction index[9].

The protocol was aimed at the comparative laboratory analysis of the inflammatory markers at the time points considered of greatest clinical significance as follows: the pre-operative period, with no drug, when those markers should not be altered; five minutes after aortic unclamping, characterizing the myocardial reperfusion time point due to recirculation of superoxide radicals to the venous sinus, and, consequently, to the right atrial cavity, which was the collection site for the next time points; 12 and 24 hours after surgery (for the inflammatory mediators), and 48 hours after surgery (for CRP).

The analysis of the biomarkers does not have a predetermined pattern. Studies with several protocols have assessed markers involved in the pathophysiology of the inflammatory response, which still lacks effective preventive management. Currently, the substances assessed on trials have not proved to completely reduce the inflammatory complications in CABG-ECC[10,11].

The descriptive analysis of the drugs used as standard treatment showed no difference between the groups in the pre-operative period. It is worth noting that, in the post-operative period, neither clinical complications occurred nor support with amines, transfusions or any other supplementary therapy was required.

The descriptive analysis of the baseline clinical and inflammatory variables showed no significant change between the groups. This draws attention to studies relating high pre-operative levels of inflammatory markers to post-operative complications, suggesting that those levels should be normal prior to surgery[12,13].

The analysis of the variables regarding the surgical treatment showed no significant difference between the groups. When extending the analysis to compare the Tmz and placebo groups of this study with those of the study by Martins et al.[6], those variables showed no significant difference.

Of the surgical variables analyzed, the ECC time and aortic cross-clamping time were similar between the groups and were also lower than those described in the literature[10,14]. Bucerius et al.[15], in a clinical trial, have recognized the ECC time as an independent predictor of post-operative complications. Nissinen et al.[16] have established a list of major complications, such as post-operative morbidity and stroke, correlating them with the ECC and aortic cross-clamping times.

When assessing the variations in C3 and C5 in the pre-operative period and at aortic unclamping, the mean levels in the groups reached a peak at the latter, followed by level drops at 12 and 24 hours. The Tmz and Placebo groups did not significantly differ, showing the same evolution reported by Tárnok et al.[17], when comparing patients operated on with and without ECC.

Previous studies have shown that CABG causes the following: a reduction in the serum levels of C3 and C5, with a concomitant increase in the serum levels of C3a, C3b and C5a; an increase in histamine and IL8; and a reduction in the peripheral blood levels of neutrophils, eosinophils and basophils, most likely due to their migration to the subendothelial tissue stimulated by the inflammatory response[4,18,19].

Chakraborti et al.[7] have assessed the concept that the ischemia and reperfusion injuries play a fundamental role in mediating complement activation. The membrane attack complex (MAC), which is formed at the end of the complement activation pathways, is more rapidly observed when reperfusion occurs. The association between neutrophil, endothelium and complement, the effect of complement on neutrophil adherence and infiltration, and the relationship between complement, mitochondria and ischemia followed by reperfusion are topics approaching the relationship of reperfusion and the activation of complement pathways in oxidative stress. Complement activation is considered to play a fundamental role in the initial phase of the inflammatory response in CABG-ECC.

Trials assessing the evolution of IL6 and IL8 levels in CABG with and without ECC have shown significantly lower levels when ECC is not used. In this study, IL6 levels were significantly reduced in the Tmz group from reperfusion onwards, that is, at the time point where a great oxidative stress occurred, five minutes after aortic unclamping. After that collection, IL6 reached its maximum level in 12 hours, declining in the following 24 hours. TNF-α was not observed at any collection time, similarly to that which was observed in other studies[20,21].

Table 1 - Clinical variables according to the groups (Tmz and Placebo)

Variable	TMZ		Plac		p value
	n	%	n	%	
Male sex	10	66.7	12	80.0	0.34
Age in years (mean ± SD)	59.0 ± 7.8		59.3 ± 5.8		0.91 [a]
Three-vessel disease [b]	11	73.3	10	66.7	0.50
Diabetes mellitus	2	13.3	2	13.3	0.70
SAH	9	60.0	10	66.7	0.50
Previous MI	3	20.0	5	33.3	0.34
Smoker or ex-smoker	7	46.7	10	66.7	0.23
SD: standard deviation.					

SAH: Systemic arterial hypertension; MI: Myocardial infarction
[a] Student t test for independent samples
[b] comparison of three-vessel and two-vessel diseases

Table 2 - Analysis of the surgical variables according to the groups

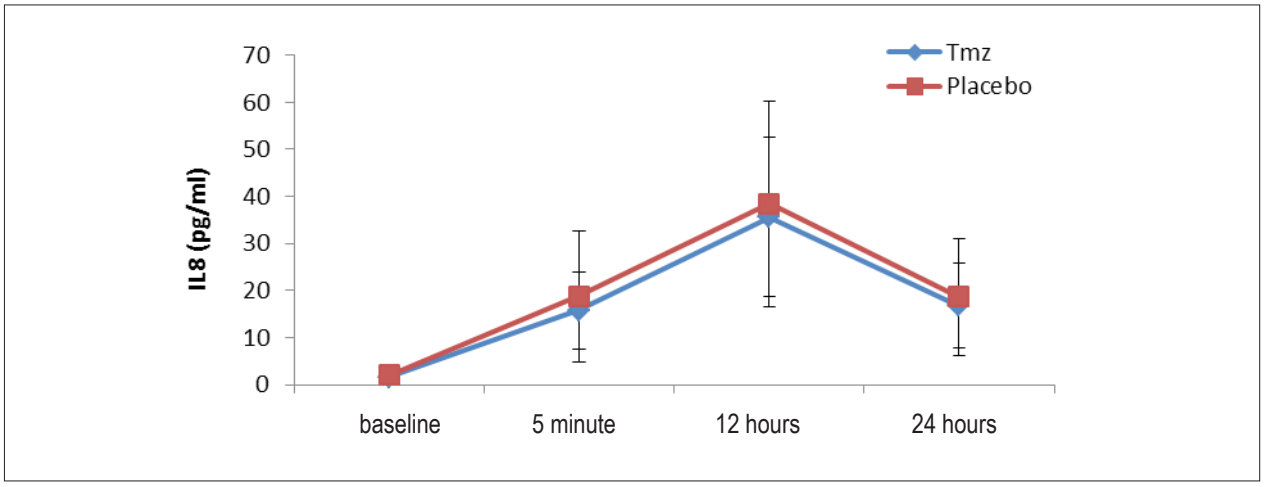
Variable	Group	n	Mean	SD	Median	Minimum	Maximum	p value
Anoxia duration	Tmz	15	66.3	23.2	58	37	120	0.22
	Plb	15	58.3	23.8	50	30	100	
ECC Time	Tmz	15	82.7	24.2	80	43	130	0.56
	Plb	15	77.3	23.1	75	50	120	
Cardiopl volume	Tmz	15	170.7	45.3	160	50	250	0.52
	Plb	15	162.7	59.3	150	100	300	
No. of grafts	Tmz	15	2.87	0.74	3.0	2	4	0.74
	Plb	15	2.93	0.59	3.0	2	4	
Hours at the ICU	Tmz	15	72.8	7.1	72	60	96	0.25
	Plb	15	78.4	14.8	72	60	120	

SD: standard deviation

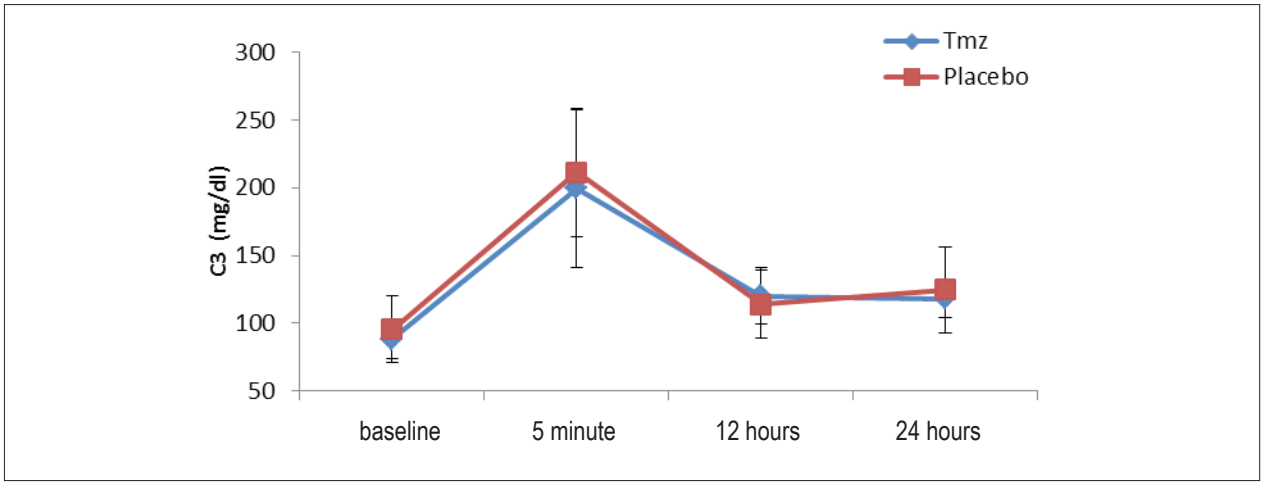
Table 3 - Comparison of the selected and non-selected patients using Tmz

Variable	Selected	n	Mean	SD	Median	Minimum	Maximum	p value
Anoxia duration	Yes	15	66.3	23.2	58	37	120	0.78
	No	15	65.5	19.0	63	34	100	
ECC Time	Yes	15	82.7	24.2	80	43	130	0.33
	No	15	74.5	19.5	75	40	110	
Cardiopl volume	Yes	15	170.7	45.3	160	50	250	0.61
	No	15	165.3	54.0	150	100	250	
No. of grafts	Yes	15	2.87	0.74	3.0	2	4	0.74
	No	15	2.93	0.59	3.0	2	4	
Hours at the ICU	Yes	15	72.8	7.1	72	60	96	0.17
	No	15	76.8	9.9	72	72	96	

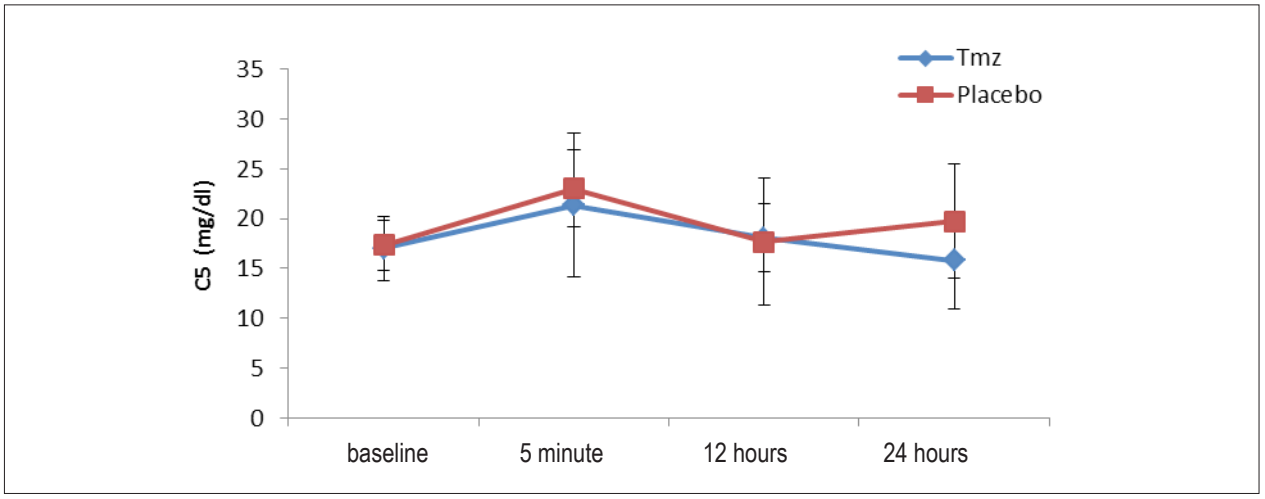
SD: standard deviation



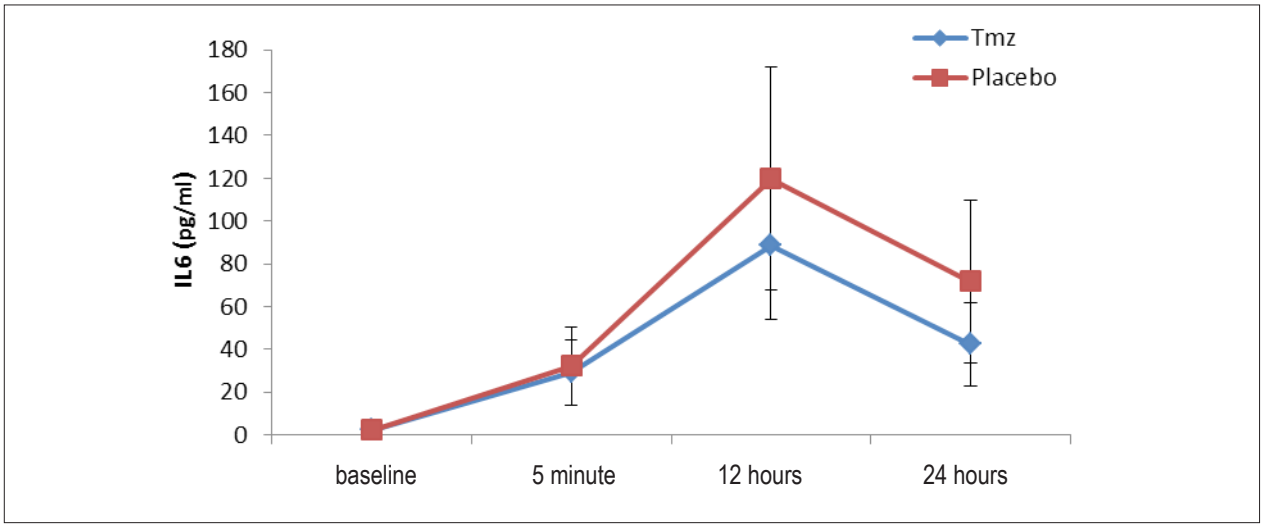
Graphic 1 - *Serum levels of interleukin 6 in the Tmz and placebo groups*



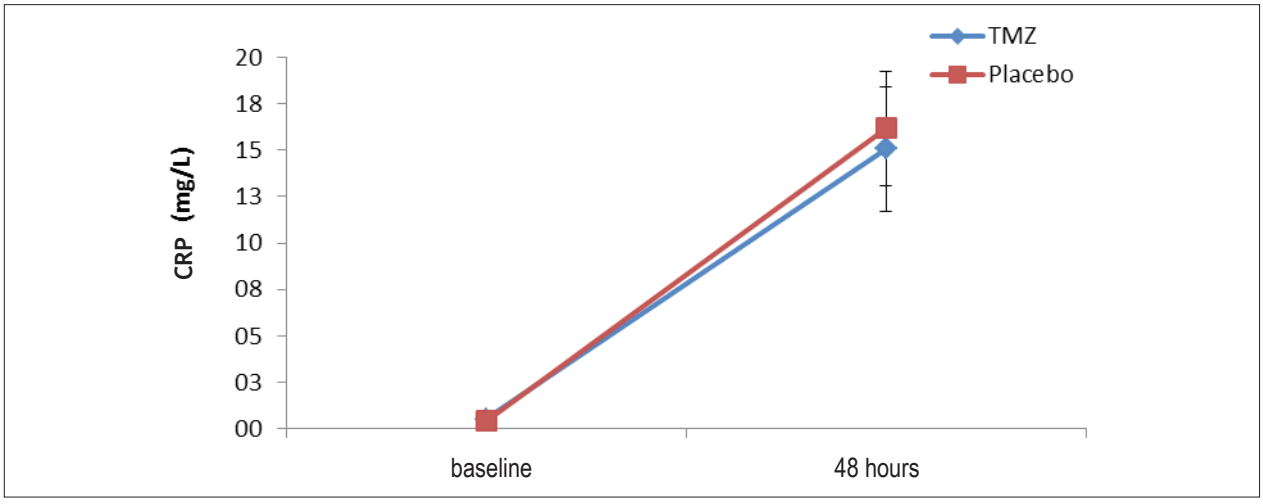
Graphic 2 - *Serum levels of complement C3 in the Tmz and placebo groups*



Graphic 3 - *Serum levels of complement C5 in the Tmz and placebo groups*



Graphic 4 - *Serum levels of interleukin 8 in the Tmz and placebo groups*



Graphic 5 - *Serum levels of HS-CRP in the Tmz and placebo groups*

The mean IL8 level did not reach a statistically significant difference (p=0.94), that is, IL8 levels in the groups progressed very similarly.

The ischemic and reperfused myocardium proved to be a major source of IL6, IL8 and TNF-α during CABG-ECC[22]. A marked increase in IL6 and IL8 levels appear during and immediately after ECC. Its peak concentration occurs a few hours after the end of CABG-ECC, with a gradual reduction to normal levels in the following 24 hours[23]. The characteristic release of IL6 and IL8 in ECC has been demonstrated after hypothermic and normothermic surgery, but no increase in TNF-α levels occur in normothermic surgery, the results of TNF-α levels in ECC being still conflicting[20,21,24].

Of the pathophysiological aspects assessed in cardiovascular surgeries, the deleterious effects of ECC on the body stand out. Several reviews of prospective and randomized trials and meta-analyses of randomized trials have compared the pro- and anti-inflammatory effects of that procedure, and have evidenced the smaller inflammatory damages in procedures without ECC. However, no reduction in the major clinical outcomes, such as mortality, stroke, myocardial infarction, and need for reintervention, has been observed[1,11,25-27].

Pintar and Collard[21] have emphasized the activation mechanisms of C3a and C5a, IL6 and IL8, TNF-α, leukotrienes, and endotoxins. They have also reported a significant increase in endothelin-1 levels, a peptide derived from the endothelium that stimulates neutrophil activation and accumulation.

Trimetazidine has a protective effect on the cardiac cell against the ischemia and reperfusion injury, leading to a reduction in the markers of myocardial aggression, of oxidative stress, and, thus, of inflammatory response[6,28]. In this clinical trial, which evidenced significant differences in the IL6 levels in the Tmz group as compared with those in the placebo group, a tendency towards lower C3 and C5 levels was observed,

with no statistically significant reduction in the groups. This can be justified by the reduced size of the sample and the fact that blood collection at the third time point of the protocol was performed 12 hours after aortic unclamping, and that the complements varied at a shorter interval.

The HS-CRP levels in the pre-operative period and 48 hours after surgery did not significantly differ between the Tmz and Placebo groups (p=0.31), evolving similarly throughout the treatment. The baseline levels in both groups were within the normal range, and the 48-hour levels were over 5 mg/L.

Studies on the clinical value of CRP levels were, at first, directed to follow-up and therapeutic control of inflammatory processes. Its role as an acute phase protein is due to its presence in many points of the inflammatory pathway. Produced and released by the liver cell, a production by the arterial wall has been also postulated. Its formation is stimulated by IL1 and IL6, and it is released by macrophages after phagocytosis of the antigen. In the past ten years, the CRP role in the atherosclerotic cardiovascular disease received more attention, CRP tending to become a risk marker of that clinical condition[29,30].

In a prospective study, Lorenzo et al.[31] have assessed patients undergoing CABG-ECC, measuring CRP as a risk marker after CABG-ECC. Those authors have investigated the association between pre-operative CRP levels and death after surgery. Levels over 3mg/dL have been considered predictive in the absence of infectious or inflammatory findings. Mezzomo et al.[32], studying patients who had undergone CABG-ECC, have concluded that pre-operative HS-CRP levels over 3 mg/L were an independent predictor of post-operative respiratory infection. Balciunas et al.[13], in a prospective study, have reported that CRP is a predictor of post-operative complications when serum levels over 3.3 mg/L are achieved. In the present study, no post-operative complications were observed in the groups during the follow-up period until hospital discharge (15 days). In addition, neither a longer ICU length of stay nor the use of vasoactive amines was required in the presence of CRP levels over those reported by Serrano et al.[11].

Figueiredo and Martin-Neto[33] have shown that Tmz is a useful drug to manage the inflammatory response following coronary angioplasty (PTCA). Those authors have reported that the pre-operative treatment with oral Tmz for three days reduced significantly the elevation in inflammatory markers before and right after PTCA.

Di Napoli et al.[34] have assessed the impact of Tmz on CRP levels in the chronic ischemic heart disease. Patients who had received that drug for 18 months maintained their plasma CRP levels unaltered as compared with those of the placebo group. Those authors have suggested that such anti-inflammatory effect could relate to the significant reduction in mortality and in hospital readmissions observed after 48 months of treatment with Tmz.

CABG-ECC seems to be the best model to associate inflammation with the effect of ischemia and reperfusion, when attempting to protect the isolated heart during prolonged asystole. Thus, the additional effect of Tmz in that process was assessed as a pre-treatment. Experimental clinical trials in that area have shown that Tmz has a direct anti-ischemic effect, limiting the accumulation of calcium, acidosis, production of superoxide radicals, and inflammation, leading to clinical benefit[6,33,34].

This study had some limitations. The first relates to the size of the sample. Although similar to other studies assessing inflammatory markers before and after CABG-ECC, the evaluation of a larger population could provide more consistency and sustainability to the results. The second limitation relates to the temporal evaluation of some markers, such as IL6 and IL8, which can peak after ECC at intervals shorter than 12 hours, and C3 and C5, which can also be elevated four hours after ECC. Regarding the protocol with blood collections at 12-hour intervals, the results replicate those of some experimental studies with animals and humans using similar methodology. It is worth considering, for future studies, the use of other methodologies of myocardial protection, such as anterograde and retrograde continuous, normothermic cardioplegia.

Conclusions

The results of this study showed a significant reduction in IL6 levels, evidencing that Tmz can be effective in reducing the inflammatory response when administered as a pre-treatment for patients undergoing CABG-ECC. The same effect, however, was not observed for the other mediators assessed, such as IL8, TNF-α, C3 and C5, and HS-CRP.

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Potential Conflict of Interest

The authors declare no conflict of interest.

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Study Association

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