An investigation of the effectiveness of oral cyclosporine on perioperative myocardial injury (PMI) in patients who undergo the surgical procedure of coronary artery bypass graft (CABG): A Randomized Controlled Clinical Trial

Seyed Mohammad Hassan Adel¹, Mohammad Ali Sheikhi², Marziyeh Dorra³

¹Departments of Cardiology and ²Cardiac Surgery, ³Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ABSTRACT

Background: Routine clinical strategies for the prevention of myocardial infarction (MI) during the surgical procedure of CABG include cross-clamp fibrillation and cardioplegia have failed to decrease the risk of perioperative myocardial injury (PMI). Cyclosporine-A (CsA) might be able to prevent mitochondrial dysfunction and PMI. Methods: In the present clinical trial, patients were divided into two groups (Case receive 2.5 mg/kg CsA and Control receive a placebo) randomly. Moreover, patients were controlled by placebo through a double-blind, single-center trial 4-12 h before anesthesia. Perioperative blood tests include bilirubin, complete blood count, the amount of hemoglobin in whole blood, liver transaminases, and glomerular filtration rate (GFR). Blood samples were taken before surgery and at 24, 48, and 72 h after surgery and serum Troponin-I and CK-MB levels were determined in all blood samples using ELISA. Results: There were no significant differences between the two groups in the results of routine pre-operative blood results, intraoperative variables, and baseline characteristics (P > 0.05). There are significant correlations between cross clamp time and cTnI and CKMB levels in patients taking CsA. In patients with both diabetes and hypertension, postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24, 48, and 72 h (P < 0.05). Moreover, patients with old MI, both postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24 h and 48 h (P < 0.05). Conclusions: In patients with a long cross-clamping period, using an oral CSA single dose before conducting CABG surgery, the risk of PMI could be decreased. Also, oral CsA has protective effect for CABG in diabetic patients with hypertension.

Keywords: CABG, clinical trial, Cyclosporine A, perioperative myocardial injury

Introduction

In developed countries, one of the main reasons for cardiovascular diseases that cause death is coronary heart disease (CHD). In a similar way, in developing countries, CHD could cause such diseases that are difficult to treat and impose high costs for individuals and society. Nearly in all patients with multivessel coronary artery disease, one of the most effective treatment options for revascularization is CABG surgery. In these patients, conducting routine CABG surgery decreases the perioperative risk of surgery. Anyway, recently, it’s proved that any increase in the

Address for correspondence: Dr. Seyed Mohammad Hassan Adel, Department of Cardiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail: dr.hassan.adel@gmail.com

Received: 05-08-2020 Revised: 29-10-2020 Accepted: 26-12-2020 Published: 27-02-2021

Access this article online

Quick Response Code: Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1598_20

How to cite this article: Hassan Adel SM, Sheikhi MA, Dorra M. An investigation of the effectiveness of oral cyclosporine on perioperative myocardial injury (PMI) in patients who undergo the surgical procedure of coronary artery bypass graft (CABG): A Randomized Controlled Clinical Trial. J Family Med Prim Care 2021;10:675-80.
prevalence of hypertension, and diabetes, and the aging population increases the rate of perioperative risks, perioperative myocardial injury (PMI), and worse clinical symptoms. The most important reasons are related to the cardiomyocyte damages caused by acute ischemia-reperfusion injury (IRI), CPB induced inflammatory injury and direct myocardial damage due to the surgery and coronary micro-embolization. Two main strategies of myocardial protection are blood cardioplegia and cross-clamp fibrillation that unfortunately have not fully succeeded in reducing PMI risks. Consequently, aiming to improve clinical outcomes, there is a high need for novel therapeutic strategies for restricting PMI risks and preserving the normal left ventricular ejection fraction (LVEF). Additionally, in patients undergoing CABG surgery, the serum levels of cardiac enzymes such as cardiac troponin T (cTnT), cardiac troponin I (cTnI), and creatine kinase-MB (CK-MB) have a significant role in determining the magnitude of PMI risks and also associated with worse short and long-term prognosis among them. As demonstrated by Venugopal et al., the opening of the mitochondrial permeability transition pore (MPTP) could cause mitochondrial dysfunction and consequent cardiomyocyte death during acute IRI. Based on some clinical and experimental studies, MI limitation and MPTP opening could be prevented by Cyclosporin A (CsA) at the onset of reperfusion. The current randomized controlled clinical trial is mainly aimed to determine the capability of oral CsA in decreasing perioperative myocardial injuries in patients who undergo CABG surgery.

**Methods**

**Study design and participants**

A randomized double-blind placebo-control (RDBPC) single-center trial was conducted at the Golestan Hospital of Ahvaz University of Medical Sciences, Ahvaz, Iran. The protocol of this study was approved by the Ethics Committees of Ahvaz University of Medical Sciences and Golestan Hospital was implemented according to the Declaration of Helsinki (DoH). The recruiting process was carried out only amongst consecutive adults who were attended the hospital for CABG surgery from February 2016 and February 2017. All the participants were informed about the trial aim, then their written consent was obtained. After that their medical history, laboratory analyses, and physical examination were recorded. The exclusion criteria of the study were: patients older than 85 years, patients with liver disease, unstable angina, myocardial infarction within two weeks of screening, patients with immunocompromised disorders, elevated liver enzymes (the enzyme of alanine aminotransferase (ALT) more than three times the upper reference limit), and kidney failure (glomerular filtration rate (GFR) of less than 45 mL/min/m2). Moreover, patients who take derivatives of xanthine or dipyridamole and glibenclamide or nicorandil were excluded from the study for their role in interfering with preconditioning.

**Randomization and masking**

The process of randomized assignment of patients (1:1) to pretreatment with either placebo or CsA was performed through a randomization sequence generated by an independent computer (Department of Medicine, Ahvaz University of Medical Sciences, Ahvaz, Iran) and opaque numbered envelopes were used for the allocation of blinded treatment by one of the investigators. Aiming to allocate treatments, all the staff, statisticians, and patients were equipped with masks. CsA capsules were over encapsulated under manufacturing practice conditions to obtain masking.

**Procedures**

The process of patient's allocation was carried out randomly for receiving 2.5 mg/kg placebo of CsA, 4-12 h before anesthesia. Normal general anesthesia induction and maintenance was performed on all patients. The results of routine preoperative blood tests included bilirubin testing, liver transaminases, GFR, complete blood count, and measurements of hemoglobin. Blood samples were taken before surgery at specific time periods of 24, 48, and 72 hours after surgery, then the serum Troponin-I (RapiCard™ InstaTest Troponin I kit - Woodland Hills, California, USA) and CK-MB (AccuDAD™ CK-MB ELISA Kit- Woodland Hills, California, USA) levels were determined in all blood samples using ELISA test according to manufacturer's protocol.

**Statistical analysis**

This study was aimed to assess the role of oral cyclosporine in the protection of patients with myocardial injuries through assessing serum CK-MB and cTnI as two main indicators of the MI magnitude. Statistical analysis was carried out with (SPSS) version 22. To compare continuous and categorical variables, the T-test and χ2 tests were administered, respectively. The achieved information is presented as mean ± SD or SEM. The significance threshold was determined statistically as P < 0.05 and all reported P values were two-tailed and the sample size was determined based on previous studies and using Med-Calc software with an error of 5% and the power of 92%, which led to a total of 46 patients.

**Results**

Primarily, a total of 88 patients undergoing CAPG were found to be eligible for recruitment to the study. However, 28 patients dropped out for meeting exclusion criteria. As could be seen from Figure 1, in the final step, 60 patients were chosen randomly for treatment (for each of placebo and CsA options, 30 patients were selected). For comprehensive analysis of quantitative and qualitative variables, two separate tables were drawn. Based on the data presented in Tables 1 and 2, between these two groups, there were no significant differences between the two groups in the results of routine pre-operative blood results, intraoperative variables, and baseline characteristics. After releasing the aortic cross-clamp, the serum levels of CsA in 12 patients were assessed immediately, and it declared that it was in the therapeutic range (531 ± 154 ng/ml).

Mean comparison of cTnI and CKMB before surgery and on the 24, 48, and 72 h postsurgical day in drug and placebo
Adel, et al.: Oral cyclosporine A on perioperative myocardial injury in patient undergoing coronary

18.09
0.434
0.667

Ex vivo studies on human heart tissue also demonstrated that CsA has cardio protective effects following IRI stimulation in isolated human atrial trabecular tissue. Several studies have shown that impaired mitochondrial permeability due to opening of mitochondrial transition pore (MPTP), is a determining factor for cardiomyocytes death in acute cardiac IRI. Studies on animal models have reported that CsA reduces the MI size. Ex vivo studies on human heart tissue also demonstrated that CsA has cardio protective effects following IRI stimulation in isolated human atrial trabecular tissue. As demonstrated by Piot et al., in STEMI patients, MI size could be limited using a single intravenous bolus of cyclosporine about 10 minutes before the PPCI procedure.

The most recent update of clinical trials in this regard was carried out by Hausenloy et al. who demonstrated that using a single dose of intravenous CsA before conducting the CABG procedure could decrease PMI in higher-risk patients with longer time of operation, cardiopulmonary bypass, and aortic cross-clamp time. In this clinical trial, the effect of oral CsA in patients undergoing CAGB surgery was investigated. The data achieved from the present study demonstrated that using a single dose of oral CsA (2.5 mg/kg) before the surgery,

Discussion

Direct manipulation of heart tissues, reperfusion, cardiopulmonary bypass, and micro-embolization of coronary arteries are common known causes of myocardial injuries during CAPG. Several studies have shown that impaired mitochondrial permeability due to opening of mitochondrial transition pore (MPTP), is a determining factor for cardiomyocytes death in acute cardiac IRI.

88 patients undergoing CAPG assessed for eligibility
9 did not meet the inclusion criteria
3 did not agree to sign the consent
2 for logistical reasons
74 patients randomized

37 assigned to receive oral CsA
37 assigned to receive oral placebo
6 refused to continue
1 passed away
5 refused to continue
2 did not show CsA in therapeutic range
30 completed study and were included in analysis
30 completed study and were included in analysis

Table 1: Preoperative and postoperative qualitative variables

| Variable | Group | Standard deviation | Mean | t-statistics | P     |
|----------|-------|-------------------|------|--------------|-------|
| Age      | Drug  | 9.47              | 60.57| -0.014       | 0.989 |
| BMI      | Placebo | 9.00             | 60.60|               |       |
| GFR      | Drug  | 20.87             | 86.54| 0.434        | 0.666 |
| Postoperative EF | Placebo | 22.61            | 84.10|               |       |
| Preoperative EF | Drug  | 9.51              | 46.05| 0.363        | 0.718 |
| Postoperative EF | Placebo | 8.80             | 45.00|               |       |
| Preoperative Hb | Drug  | 2.01              | 12.62| -0.193       | 0.848 |
| Postoperative Hb | Placebo | 1.86             | 12.72|               |       |
| Preoperative WBC | Drug  | 2558.60           | 8023 | -0.941       | 0.351 |
| Postoperative WBC | Placebo | 3457.57          | 8763 |               |       |
| Preoperative BUN | Drug  | 5.37              | 17.37| -0.806       | 0.423 |
| Postoperative BUN | Placebo | 7.85             | 18.77|               |       |
| Preoperative BUN | Drug  | 8.36              | 20.97| -0.033       | 0.974 |
| Postoperative BUN | Placebo | 7.12             | 21.03|               |       |
| Preoperative CV | Drug  | 0.18              | 0.89 | -0.884       | 0.380 |
| Postoperative CV | Placebo | 0.20             | 0.94 |               |       |
| Preoperative CV | Drug  | 0.29              | 0.95 | -1.009       | 0.317 |
| Postoperative CV | Placebo | 0.25             | 1.02 |               |       |
| Preoperative Hb | Drug  | 0.41              | 0.89 | 1.110        | 0.271 |
| Postoperative Hb | Placebo | 0.29             | 0.79 |               |       |
| Preoperative BUN | Drug  | 0.29              | 0.93 | 1.074        | 0.287 |
| Postoperative BUN | Placebo | 0.20             | 0.86 |               |       |
| Preoperative ALP | Drug  | 7.98              | 22.83| -1.362       | 0.178 |
| Postoperative ALP | Placebo | 11.59            | 26.33|               |       |
| Preoperative ALP | Drug  | 7.56              | 23.70| -0.684       | 0.496 |
| Postoperative ALP | Placebo | 12.58            | 25.53|               |       |
| Bypass time | Drug  | 28.57             | 80.68| 1.329        | 0.190 |
| Postoperative Bypass time | Placebo | 16.85          | 72.11|               |       |
| Cross Clamp Time | Drug  | 16.61             | 36.28| 0.600        | 0.551 |
| Postoperative Cross Clamp Time | Placebo | 14.79          | 33.67|               |       |
| Operation Time | Drug  | 55.14             | 196.67| 0.622        | 0.536 |
| Postoperative Operation Time | Placebo | 33.52          | 189.33|               |       |
| Preoperative AST | Drug  | 18.09             | 28.63| -0.420       | 0.676 |
| Postoperative AST | Placebo | 19.36            | 30.67|               |       |
| Preoperative AST | Drug  | 18.26             | 30.77| 0.269        | 0.789 |
| Postoperative AST | Placebo | 18.23           | 29.50|               |       |

groups is shown in Table 3. Serum CKMB and cTnI levels on the first postsurgical day were at their pick level in both patient groups, showing PMI occurrence during the surgery. The mean comparison of both CKMB and cTnI levels in postsurgical days show a more decrease in patients receiving oral CsA than placebo group. However, the results are not statistically significant.

Ameliorative correlation between reduction of both Troponin and CKMB with operation time in drug group was shown in Tables 4 and 5. We also found that there are significant correlations between cross clamp time and cTnI and CKMB levels in patients taking CsA [Tables 4 and 5]. Results also indicate that in patients with diabetes and hypertension, postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24, 48, and 72 h [Table 6]. Moreover, in patients with MI history, both postsurgical cTnI and CKMB levels decrease significantly in CsA compared to placebo group on 24 h and 48 h [Table 6].
Our results indicate that oral CsA has protective effect for CABG in coronary artery bypass graft surgery.\cite{10} Our results indicate that administration of oral CsA in patients with both diabetes and hypertension significantly reduces post-operative levels of both cTnI and CKMB that might be further protective, improve the surgery outcomes and morbidity rate in these patients.

In their study Bottle \textit{et al}.\cite{10} investigating the preoperative risk factors in patients with a prior myocardial infarction who undergo CABG procedure. The declared that there is a close association between perioperative risks and myocardial infarction. In present study, we found that postoperative levels of both cTnI and CKMB patients receiving oral CsA are significantly reduced.

**Conclusion**

In conclusion, considering the limitations such as the relatively small sample size, lack of information about the major adverse cardiovascular events (MACE), and normal LVEF, we demonstrated that using a single dose of oral CsA before conducting the CABG procedure could effectively decrease PMI risks in patients with long cross-clamp and operation time. We also indicated that oral CsA has protective effect for CABG in diabetic patients with hypertension.

**Acknowledgements**

Our sincere thanks also go to all staff of the department of cardiovascular surgery and the central laboratory of Golestan Hospital for providing us with the opportunity of joining their team as an intern and also the access to all facilities and laboratories.
Table 5: Correlation between operation time, cross clamp time and Troponin levels in Tow groups

| Group      | Variables | Indexes                        | Troponin Ratio 24 h after to 24 before | Troponin Ratio 48 h to 24 h | Troponin Ratio 72 h to 48 h | Troponin Ratio 72 h to 24 h |
|------------|-----------|--------------------------------|--------------------------------------|----------------------------|------------------------------|-----------------------------|
| drug group | Operation | Correlation Coefficient        | 0.435*                                | -0.383*                    | -0.255*                     | -0.530**                    |
|            | Time      | P                              | 0.016                                 | 0.036                      | 0.049                       | <0.001                      |
|            | Number    |                                | 30                                    | 30                         | 30                          | 354                         |
| placebo    | Operation | Correlation Coefficient        | 0.463*                                | -0.383*                    | -0.290*                     | -0.586**                    |
| group      | Time      | P                              | 0.010                                 | 0.036                      | 0.032                       | 0.001                       |
|            | Number    |                                | 30                                    | 30                         | 30                          | 30                          |

Table 6: Mean comparison of Troponin levels and CKMB in diabetic patients with hypertension and Also MI History patients in two groups

| Variable            | Co-Exist disease | Time      | Group | Number | Mean   | Standard deviation | P     |
|---------------------|------------------|-----------|-------|--------|--------|--------------------|-------|
| Troponin            | diabetic patients | Before operation | Drug  | 24     | 1.18   | 0.35               | 0.812 |
|                     | with hypertension| 24 h      | Drug  | 24     | 1.99   | 0.75               | 0.038*|
|                     |                  | 24 h      | Placebo | 21     | 1.21   | 0.36               |        |
|                     |                  | 48 h      | Drug  | 24     | 1.67   | 0.38               | 0.037*|
|                     |                  | 48 h      | Placebo | 21     | 2.16   | 0.79               |        |
|                     |                  | 72 h      | Drug  | 24     | 1.62   | 0.41               | 0.009*|
|                     |                  | 72 h      | Placebo | 21     | 2.07   | 0.46               |        |
| MI history          | Before operation | Drug  | 11     | 16.70  | 5.04   | 0.579              |        |
| CKMB                | diabetic patients | 24 h      | Placebo | 11     | 16.60  | 4.08               |        |
|                     | with hypertension| 48 h      | Drug  | 11     | 23.70  | 3.79               | 0.043*|
|                     |                  | 48 h      | Placebo | 11     | 27.80  | 2.00               |        |
|                     |                  | 72 h      | Drug  | 11     | 19.60  | 5.04               | 0.205 |
|                     |                  | 72 h      | Placebo | 11     | 24.00  | 4.08               |        |
|                     | Before operation | Drug  | 11     | 16.70  | 5.04   | 0.579              |        |
|                     | MI history       | 24 h      | Placebo | 11     | 16.60  | 4.08               |        |
|                     |                  | 48 h      | Drug  | 11     | 23.70  | 3.79               | 0.043*|
|                     |                  | 48 h      | Placebo | 11     | 27.80  | 2.00               |        |
|                     |                  | 72 h      | Drug  | 11     | 19.60  | 5.04               | 0.205 |
|                     |                  | 72 h      | Placebo | 11     | 24.00  | 4.08               |        |

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
Financial support and sponsorship

The present study was supported by the Research, Technology, and Development Deputy of Ahvaz Jundishapur University of Medical Sciences. The cost of this article has been provided from the credit of the research project thesis with approved Issue number CVRC-9504.

Conflicts of interest

There are no conflicts of interest.

References

1. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010;35:72-115.
2. Allen NB, Zhao L, Liu L, Daviglus M, Liu K, Fries J, et al. Favorable cardiovascular health, compression of morbidity, and healthcare costs. Circulation 2017;135:1693-701.
3. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: A historical perspective. Lancet 2014;383:999-1008.
4. Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: Meta-analysis of randomized clinical trials of the arterial grafting and stenting era. JAMA Intern Med 2014;174:223-30.
5. Venugopal V, Ludman A, Yellon DM, Hausenloy DJ. ‘Conditioning’ the heart during surgery. Eur J Cardiothorac Surg 2009;35:977-87.
6. Thielmann M, Dörge H, Martin C, Belosjorow S, Schwanke U, van de Sand A, et al. Myocardial dysfunction with coronary microembolization. Circ Res 2002;90:807-13.
7. Croal BL, Hillis GS, Gibson PH, Fazal MT, El-Shafei H, Gibson G, et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. Circulation 2006;114:1468-73.
8. Fellahi J-L, Gué X, Richomme X, Monier E, Guillou L, Riou B. Short-and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. Anesthesiology 2003;99:270-4.
9. Hausenloy DJ, Maddock HL, Baxter GF, Yellon DM. Inhibiting mitochondrial permeability transition pore opening: A new paradigm for myocardial preconditioning? Cardiovasc Res 2002;55:534-43.
10. Hausenloy DJ, Duchen MR, Yellon DM. Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia–reperfusion injury. Cardiovasc Res 2003;60:617-25.
11. Argaud L, Gateau-Roesch O, Muntean D, Chalabreysse L, Loufouat J, Robert D, et al. Specific inhibition of the mitochondrial permeability transition prevents lethal reperfusion injury. J Mol Cell Cardiol 2005;38:367-74.
12. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Meowton N, et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 2008;359:473-81.
13. Hausenloy DJ, Boston-Griffiths E, Yellon D. Cyclosporin A and cardioprotection: From investigative tool to therapeutic agent. Br J Pharmacol 2012;165:1235-45.
14. Skyschally A, Schulz R, Erbel R, Heusch G. Reduced coronary and inotropic reserves with coronary microembolization. Am J Physiol Heart Circ Physiol 2002;282:H611-4.
15. Marzilli M, Huqi A. Cardioprotective therapy in reperfusion injury: Lessons from the European Myocardial Infarction Project—Free Radicals (EMP-FR). Heart Metab 2010;46:35-7.
16. Leung AW, Halestrap AP. Recent progress in elucidating the molecular mechanism of the mitochondrial permeability transition pore. Biochim Biophys Acta (BBA)-Bioenergetics 2008;1777:946-52.
17. Hausenloy DJ, Yellon DM. The mitochondrial permeability transition pore: Its fundamental role in mediating cell death during ischaemia and reperfusion. Academic Press; 2003.
18. Shanmuganathan S, Hausenloy DJ, Duchen MR, Yellon DM. Mitochondrial permeability transition pore as a target for cardioprotection in the human heart. Am J Physiol Heart Circ Physiol 2005;289:H237-42.
19. Clough RA, Leavitt BJ, Morton JR, Plume SK, Hernandez F, Nugent W, et al. The effect of comorbid illness on mortality outcomes in cardiac surgery. Arch Surg 2002;137:428-32; discussion 32-3.
20. Bottle A, Mozid A, Grocott HP, Walters MR, Lees KR, Aylin P, et al. Preoperative risk factors in 10 418 patients with prior myocardial infarction and 5241 patients with prior unstable angina undergoing elective coronary artery bypass graft surgery. Br J Anaesth 2013;111:417-23.