ORIGINAL ARTICLE

Impact of cyclosporine A use in the prevention of reperfusion injury in acute myocardial infarction: A meta-analysis

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Abstract

Background: *Reperfusion injury is an important limiting factor associated with revascularization in acute myocardial infarction (AMI). Various therapies have been tried in an attempt to prevent reperfusion injury, but the search has been elusive. The role of cyclosporine A (CsA) in the prevention of reperfusion injury in AMI is still not clear. The objective of this study was to find out whether CsA is beneficial in reducing reperfusion injury in acute ST elevation myocardial infarction.*

Methods: *We performed a systematic search of Pubmed, Scopus, clinicaltrial.gov, and Cochrane Database for randomized control trials (RCT) measuring the effect of CsA in AMI compared to a placebo. The Mantel-Haenszel method and random effect model were used to analyze the data. A total of 1,566 patients (776 in the CsA group and 790 in the placebo group), who participated in 5 RCTs were included in our meta-analysis.*

Results: *We did not find any significant differences between the CsA and placebo groups in terms of all-cause death (odds ratio [OR] 1.21, 95% confidence interval [CI] 0.78–1.87) and cardiovascular death (OR 1.05, 95% CI 0.66–2.49). Similarly, we did not find any significant differences in terms of cardiogenic shock, recurrent ischemia and myocardial infarction, heart failure and echocardiographic outcomes.*

Conclusions: *Cyclosporine A is not helpful in preventing reperfusion injury in AMI.* (Cardiol J 2017; 24, 1: 43–50)

Key words: myocardial infarction, reperfusion injury, cyclosporine A, mitochondrial permeability transition pore protein

Introduction

Although we have seen substantial advancement in the field of coronary artery disease, mortality rates still remain high. Reperfusion injury is an additional insult to already ischemic myocardial tissue. While percutaneous coronary intervention (PCI) attenuates the ischemic injury, it inadvertently accentuates the reperfusion injury. The opening of the mitochondrial permeability transition pore (MPTP) is one of the important mechanisms leading to reperfusion injury and cardio-myocyte death [1]. Since 1980s, cyclosporine A (CsA) has been known to inhibit opening of the MPTP [2]. Several experimental animal studies have been conducted to find the effects of CsA in reperfusion injury [3–17] and a meta-analysis, which included experimental studies in animal models involving
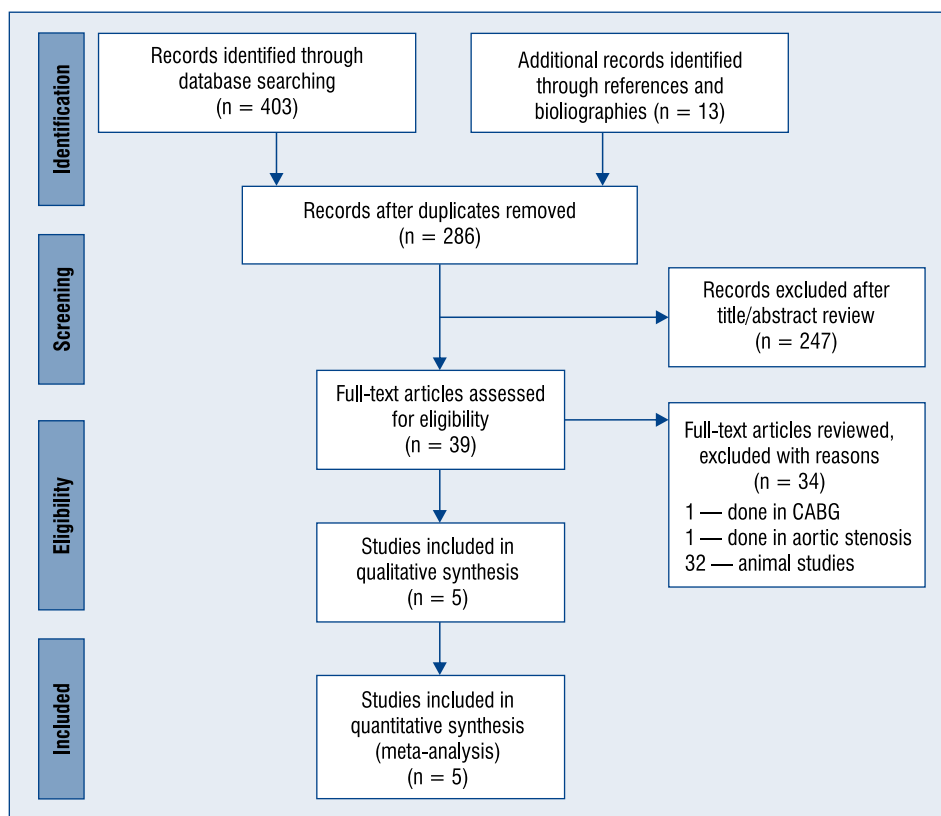
Figure 1. PRISMA diagram for the review; CABG — coronary artery bypass grafting.

CsA, showed reduced infarct size [18]. The first human study in acute ST elevation myocardial infarction (STEMI) using CsA was a small pilot study published in 2008 which showed reduced infarct size when compared to a placebo [19]. Studies published subsequently showed conflicting results [20]. We conducted this meta-analysis to find the protective effects of CsA in prevention of adverse clinical outcomes secondary to reperfusion injury.

Methods

The PRISMA statement for reporting meta-analyses and systemic reviews, as recommended by the Cochrane Collaboration, was used for this meta-analysis (Fig. 1) [21]. Our search for studies published by 30th July 2016, was conducted through Pubmed, Cochrane library databases, clinicaltrial.gov, and Scopus databases from inception. We used different strategies based on availability of Medical Subject Headings (MeSH) terms. For Pubmed and Cochrane library databases we used Mesh terms, "myocardial infarction" and "cyclosporine", connected with Boolean operator 'AND'. For Scopus and clinicaltrial.gov we used following Boolean search strategy: (Myocardial infarction OR MI OR ACS OR STEMI) AND (Cyclosporine OR Cyclosporins OR Cyclosporine A). Search strategies are elaborated on in Table 1. All results were reviewed. For our meta-analysis, we only used articles published in English. We took all measures necessary to prevent data duplication and used only published data. Publication bias was not measured due to the small number of studies analyzed.

The eligibility criteria for this meta-analysis stated that each study must: 1) include human subjects undergoing any intervention for STEMI, either percutaneous intervention or thrombolysis; 2) a randomized control trials (RCT) comparing pre-intervention CsA with a placebo; and 3) report relevant clinical or echocardiographic outcomes, whether primary or secondary. A total of 5 RCTs, which had been published in peer-reviewed journals, were included in our studies [19–24]. We extracted the baseline study details from all the selected trials (Tables 2, 3); outcomes not included in the analysis are listed in Table 4.

The clinical outcomes we measured were: all-cause death, cardiovascular death, heart fail-

Table 1. Search strategies for different databases.

Databases	Search strategy
Pubmed	(Cyclosporines [MeSH Terms]) AND (Myocardial infarction [MeSH Terms])
SCOPUS	TITLE-ABS-KEY (myocardial infarction OR ACS OR STEMI OR MI) AND TITLE-ABS-KEY (Cyclosporine a OR Cyclosporine OR Cyclosporines)
Clinicaltrials.gov	(myocardial infarction OR MI OR ACS OR STEMI) AND (Cyclosporine OR Cyclosporines OR Cyclosporine a)
Cochrane library	Mesh descriptor [Cyclosporines] AND Mesh descriptor [Myocardial Infarction]

Table 2. Baseline characteristics of the patients. Data are given in Cyclosporine group/Control group format.

	Ottani et al. 2016, CIRCUS study	Cung et al. 2015, CYCLE study	Piot et al. 2008	Ghaffari et al. 2013	Mewton et al. 2010
Number	395/396	207/203	30/28	50/51	15/13
Age	61.2/59.7	62.5/63.2	57/57	64/60.3	60/63
Male	333/323	167/160	25/21	38/46	12/8
Body mass index	26.6/26.9	27.1/26.4	26/27	N/A	27/25
Smokers	152/180	84/81	17/16	16/19	8/7
Diabetes mellitus	54/48	27/31	4/4	16/19	4/3
Hypertension	152/153	114/113	15/13	21/22	4/4
Dyslipidemia	158/154	72/83	14/12	8/6	6/4

Table 3. In-hospital strategies. Data are given in Cyclosporine group/Control group format.

	Ottani et al. 2016, CIRCUS study	Cung et al. 2015, CYCLE study	Piot et al. 2008	Ghaffari et al. 2013	Mewton et al. 2010
Aspirin	371/363	205/202	29/24	49/51	15/13
Heparin	320/327	175/171	30/28	48/51	16/11
GP IIb/IIIa antagonist	155/154	90/92	11/10	Not available	4/5
Beta-blocker	424/455	164/167	Not available	46/45	13/11
ACEI/ARBs	405/427	147/146	Not available	49/51	13/10
Anterior infarct	All anterior infarct	102/101	13/11	All anterior infarct	7/5
Primary intervention	PCI	PCI	PCI	Thrombolysis	PCI
Initial TIMI flow < 2	345/361	207/203	3/1	Not applicable	2/1
TIMI flow after PCI or thrombolysis	2.68/2.86	2.82/2.88	2.7/2.7	2.63/2.78	2.7/2.8
Stent implanted	323/338	198/195	30/28	NA	16/11

ACEI/ARBs — angiotensin converting enzyme inhibitor/angiotensin receptor blockers; GP — glycoprotein; PCI — percutaneous intervention; TIMI — Thrombolysis In Myocardial Infarction

ure, cardiogenic shock, recurrent ischemia and myocardial infarction, and major arrhythmias. We also measured echocardiographic outcomes: left ventricular ejection fraction (LVEF), left ventricular end-systolic volume and left ventricular end-diastolic volume. All of the outcomes were calculated with RevMan, version 5.3, for Windows (Cochrane Collaboration, Oxford, United Kingdom). Using random model, odds ratios (OR) were calculated with a confidence interval (CI) of 95% and heterogeneity was calculated with I2. Mean difference and random model were used to analyze continuous data. A p-value of < 0.5 was considered significant.

Table 4. Outcomes measured in the included studies, not measured in meta-analysis.

	Outcome — median (IQR) or mean ± SD	Cyclosporine	Control	P
Cung et al., 2015	ST segment resolution*	52%	49%	0.55
CIRCLE study	High sensitivity cardiac TnT [ng/L]	2160 (1087–3274)	2068 (1117–3690)	0.85
	LV wall motion score	1.35 ± 0.35	1.34 ± 0.34	0.78
	LV akinetic/dyskinetic segments [%]	11.8 ± 14.4	12.6 ± 14	0.59
Ottani et al., 2016	ST elevation post PCI [mm]	2.7 ± 1.9	2.7 ± 1.9	NS
CIRCUS study	Peak CK [IU/L]	3992 (1910–5447)	3917 (1878–5608)	NS
	Adverse LV remodeling‡	42.8%	40.7%	0.53
Piot et al., 2010	Area under curve CK release [arbitrary unit]	138,053 (114,008–283,461)	247,930 (145,639–404,349)	0.04
	Area under curve TnI release [arbitrary units]	112,312 (48,680–153,956)	129,320 (65,019–224,116)	0.15
	Mass of infarcted tissue on MRI on day 5 [g]	37 (21–51)	46 (20–65)	0.04
Mewton et al., 2010	Infarct size at 6 month [g]	29 ± 15	38 ± 14	0.04
Ghaffari et al., 2013	Peak CK-MB [IU/L]	271.8 ± 210.1	281.7 ± 208.3	0.81
	Peak-TnI [ng/mL]	17.7 ± 11.2	18.1 ± 11.7	0.86
	% ST segment resolution at 90 min [min]†	34.8 ± 6.4	36 ± 11.2	0.51

*≥ 70% resolution of ST segment elevation at 1 h after PCI.

‡An increase of 15% or more in the left ventricular end-diastolic volume.

†The reduction of the highest ST-segment elevation in any lead by at least 50% of the initial value in the first 60–90 min of treatment.

CK-MB — creatine kinase MB fraction, IQR — interquartile range; LV — left ventricle; MRI — magnetic resonance imaging; NS — not significant; PCI — percutaneous coronary intervention; SD — standard deviation; TnI — troponin I, TnT — troponin T

Results

A total of 1,566 patients were included in our analysis, with 776 in the group which received CsA and 790 in the placebo group. We found no significant differences between the two groups in terms of LVEF (mean difference 1.21, 95% CI –0.65–3.07) and left ventricular end-systolic volume (mean difference 1.60, 95% CI –4.01–7.22). Similarly, we did not find any significant differences in left ventricular end-diastolic volume (mean difference 3.32, 95% CI –3.51–10.15) (Fig. 2). With regards to clinical outcomes, no significant differences in major arrhythmias (OR 0.84, 95% CI 0.60–1.18) or recurrent ischemia and myocardial infarction (OR 0.72, 95% CI 0.34–1.53) (Fig. 2) were found. Additionally, we did not find any significant differences when looking at all-cause death (OR 1.21, 95% CI 0.78–1.87), cardiogenic shock (OR 1.23, 95% CI 0.73–2.09), cardiovascular death (OR 1.05, 95% CI 0.66–2.49), and heart failure (OR 0.86, 95% CI 0.55–1.35) (Fig. 3).

Discussion

The goal of our study was to find out whether the use of cyclosporine before reperfusion is associated with better clinical and echocardiographic outcomes or not. We did not find any significant differences between the two groups in terms of clinical and echocardiographic outcomes. The first proof-of-concept study of CsA (Sandimmune preparation) showed a significant difference in the release of creatine kinase when comparing the CsA group to the placebo group [19]. It was thought to bring paradigm shift in the prevention of reperfusion injury. Subsequently, a larger RCT (CIRCUS study) was done, however, it failed to show any benefits in terms of primary outcome (adverse left ventricular remodeling, all-cause mortality and hospitalization for heart failure) (OR 1.04, 95% CI 0.78–1.39) [22]. As hypothesized by the authors, this was likely due to the use of a different formulation of CsA; the CIRCUS study used the CicloMulsion formulation instead of the Sandim-
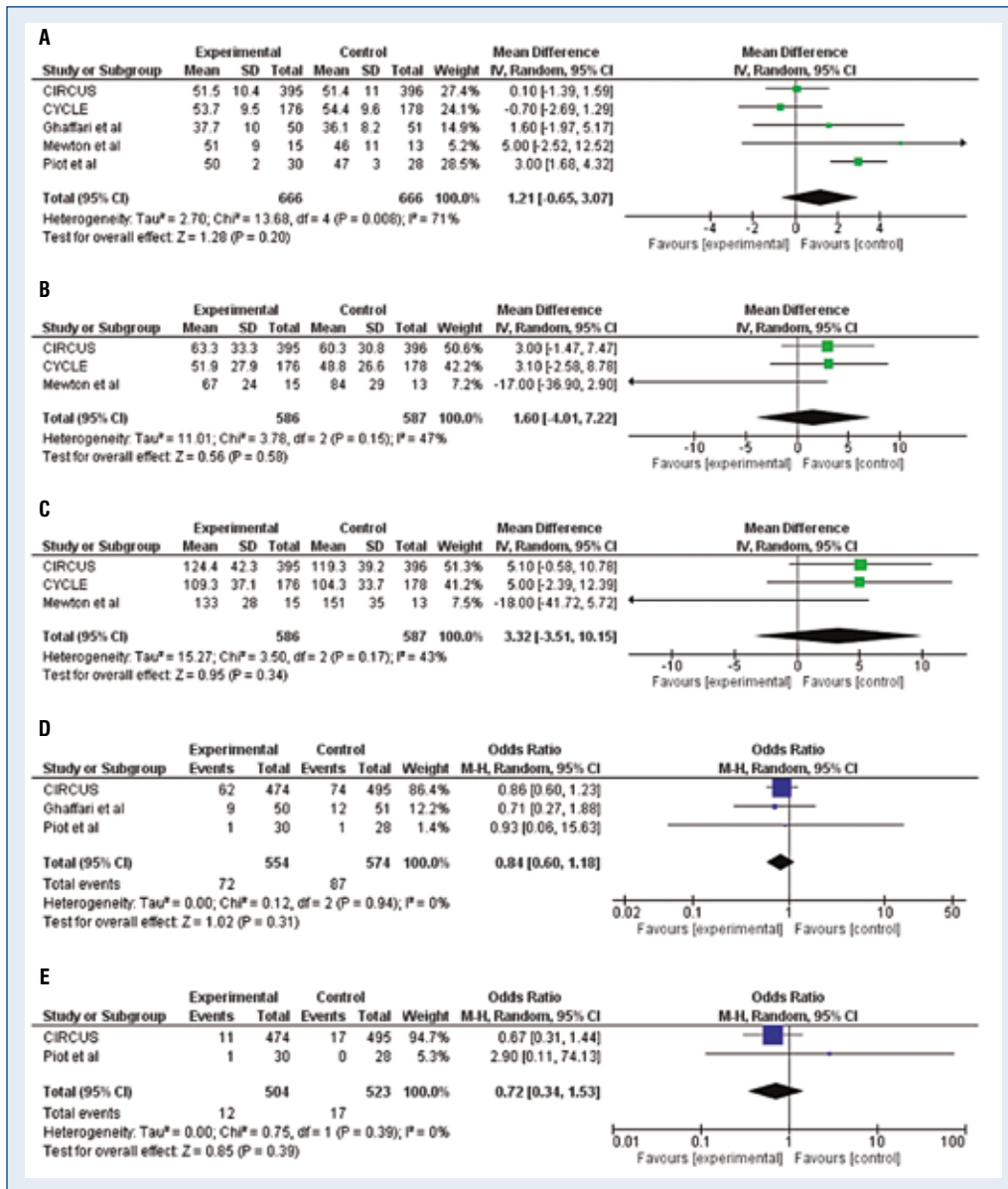
Figure 2. Forest plots of cyclosporine A versus placebo; **A.** Left ventricular ejection fraction; **B.** Left ventricular end-systolic volume; **C.** Left ventricular ejection diastolic volume; **D.** Major arrhythmia; **E.** Recurrent ischemia/myocardial infarction.

mune formulation. However, the recently published CYCLE study, which used the Sandimmune formulation, failed to show a significant difference in primary endpoint (resolution of ST-segment ≥ 70%) [20]. The CicloMulsion preparation has been found to have similar pharmacokinetics and rather fewer adverse effects compared to Sandimmune preparation [25].

A study done on patients undergoing coronary artery bypass grafting surgery found no significant difference between the peak troponin T in CsA and placebo groups, except for the high-risk group with prolonged surgery — it showed that the extent of perioperative myocardial infarction was reduced in high-risk CsA patients [26]. Another RCT done in patients undergoing surgery for aortic stenosis showed a significant difference in the area under the curves for troponin I that favored the CsA group [27]. A few studies included in our meta-analysis used ST segment resolution as a surrogate marker of the successful coronary intervention [20, 23]. It has been proven in multiple studies that early and complete ST segment resolution is associated with better outcomes [28].
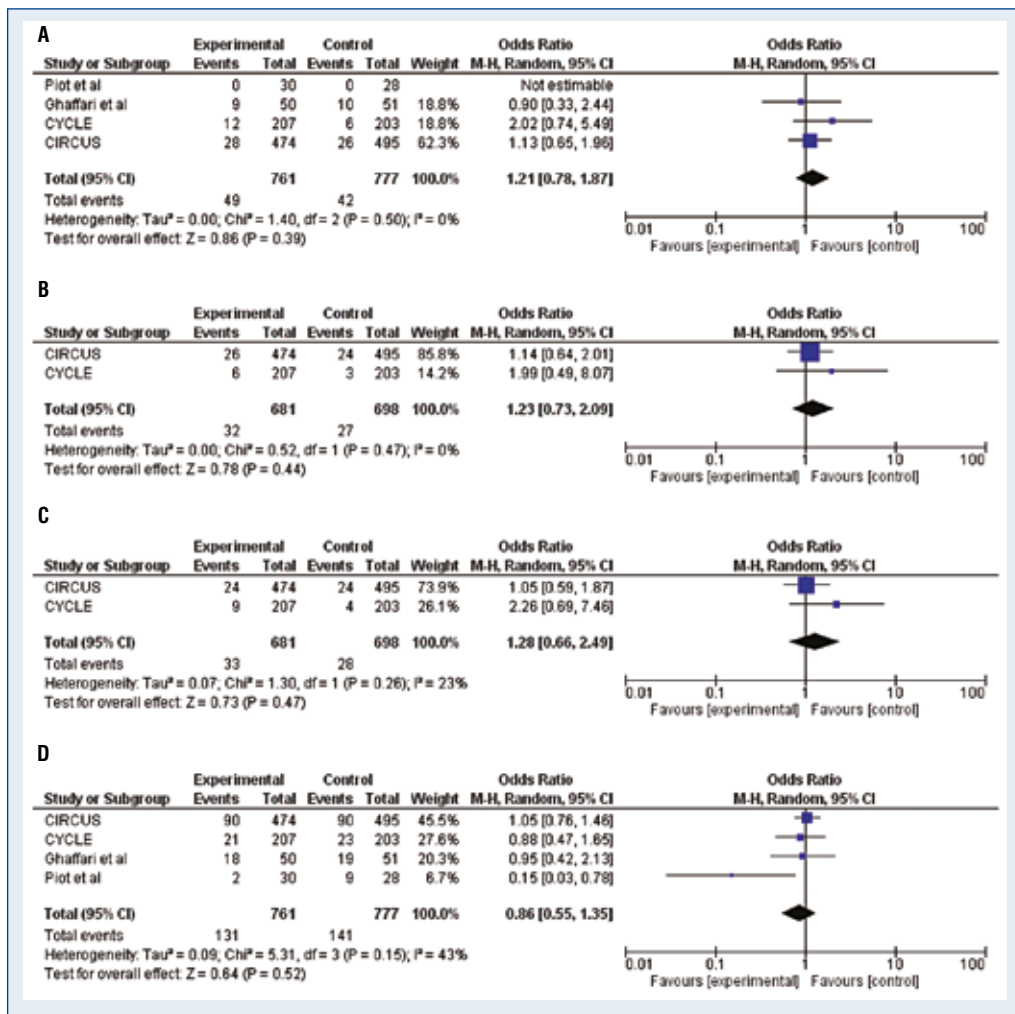
Figure 3. Forest plots of cyclosporine A versus placebo; **A.** All-cause death; **B.** Cardiogenic shock; **C.** Cardiovascular death; **D.** Heart failure.

Only the CYCLE study reported any adverse reactions to CsA. It reported a total of 5 adverse events, including one serious adverse drug reaction [20]. In all studies, CsA was given in a single injection just before the intervention. All human studies used a dose of 2.5 mg/kg.

Several small pre-clinical studies have used CsA in animal models with mechanically occluded coronary arteries. There is extensive pre-clinical evidence that use of CsA during myocardial perfusion reduces myocardial infarct size by up to 50% [29, 30]. This evidence not only regenerated the interest in reperfusion injury, but also leads to an increased understanding of the MPTP and Reperfusion Injury Salvage Kinase (RISK) pathway. In disagreement with animal studies, most of the clinical studies failed to show any benefit to using CsA in STEMI patients.

The failure of this translation is likely due in part to the poor methodology of the pre-clinical studies. No best practice standards exist for animal trials, which tend to lack statistical robustness. Most of the animal studies had a very small sample size. Furthermore, only a few studies calculated the sample size [6, 31] and most did not disclose conflicts of interests [18]. Additionally, while most of the studies were done in rodents [18], the majority of those done in pigs showed cyclosporine fail to decrease infarct size [3, 31]. This striking difference between two animal species indicates the existence of variation in the mechanism of reperfusion injury between species. This concern appears more compelling in light of evidence from experiments showing that pigs, unlike rodents, do not need RISK pathway activation for protection from reperfusion injury [32, 33].

Another important root cause of failed translation is the inability of animal models to mimic the human pathology. Unlike animals, the human subjects in most trials had numerous comorbidities. The humans also were taking different medications which might interfere with reperfusion. Additionally, disease models in animal studies are created by mechanical occlusion of relatively healthy coronary arteries. Human subjects, however, have thrombus formation secondary to plaque rupture in atherosclerotic coronary arteries.

Finally, cyclosporine has unique pharmacodynamic and pharmacokinetic properties. Cyclosporine is mainly metabolized by cytochrome P450 3A4 (CYP3A4). There are more than 20 genetic polymorphisms of the CYP3A4 gene [34]. Majority of these polymorphisms leads to decrease in function of the CYP3A4. Some of these polymorphisms are expressed by up to 9% of Caucasians [34]. Moving to pharmacokinetics, experiments have shown that CsA protects against reperfusion injury at a concentration between 0.4 and 2 μmol/L [35]. However, this protective effect is lost when the concentration exceeds 5 μmol/L.

Several studies have shown 2.5 mg/kg to be the optimal dose for the best protection against reperfusion injury [36]. Contrary to this evidence, dose-dependent pro-apoptotic effects have been observed with cyclosporine in many pre-clinical studies [37]. With these considerations in mind, we believe that CsA-mediated protection is highly dose dependent and has a very narrow therapeutic index.

A recently published meta-analysis analyzed the effects of cyclosporine on the prevention of reperfusion injury in patients undergoing cardiac surgeries, PCI, and thrombolysis. It studied the effect on LVEF, creatine kinase-MB, and infarct size [38]. However, the authors did not report adverse events and mortality data. It included three of the RCTs included in our analysis, along with one RCT in patient undergoing coronary artery bypass surgery and one RCT in patient undergoing surgery for aortic stenosis [19, 23, 24, 26, 27]. Additionally, two of the larger trials comparing the effect of cyclosporine in acute myocardial infarction have been published recently and were not included in this study. This meta-analysis concluded that cyclosporine may not protect against reperfusion injury in clinical patients. The result of this meta-analysis is in concordance with our conclusion.

Conclusions

Cyclosporine A use prior to percutaneous intervention or thrombolysis failed to show any significant decrease in the clinical and echocardiographic outcomes in STEMI patients. It is time to explore new targets or other novel approaches to reduce reperfusion injury.

Conflict of interest: None declared

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