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Chapter 14

The Cardioprotection of Silymarin in Coronary Artery Bypass Grafting Surgery

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Additional information is available at the end of the chapter

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1. Introduction

Coronary artery bypass grafting surgery (CABG) is one of the most effective therapies for coronary artery disease (CAD). CABG is conventionally performed with the use of cardiopulmonary bypass (CPB), which has been associated with an increased frequency of complications [1-3]. A variety of risk factors has been described to help delineate risk assessment of patients undergoing CABG, including preoperative left ventricular ejection fraction (LVEF) [4, 5] and postoperative increase in creatine kinase myocardial band (CK-MB) levels [6-11]. In patients undergoing coronary artery bypass grafting (CABG), the use of cardiopulmonary bypass (CPB) in combination with aortic clamping during coronary artery bypass grafting (CABG) elicits ischemic myocardial injury [12]. The vascular endothelium is a complex synthetic organ subject to injury from numerous potential insults, including oxidative stress [13, 14] modified lipoproteins [15], and hemodynamic forces [16]. Injured endothelial cells initiate a largely stereotyped, initially protective response. The concurrent uptake of low-density lipoproteins (LDLs) by monocyte-derived macrophages transforms them in to the lipid laden foam cells that constitute a key element of the fatty streak, the first recognizable progenitor of the advanced atherosclerotic lesion [17, 18].

Silymarin, a flavonolignan from 'milk thistle' (Silybum marianum) plant, is used from ancient times as a hepatoprotective, antioxidant, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulatory and liver regenerating. Silymarin has cardioprotective activity against ischemia-reperfusion induced myocardial infarction in rats [19].

Protective efficacy of Silymarin treatment confirmed by anti-inflammatory and antioxidant actions against reperfusion injury and inflammation during CABG surgery [20].

This may represent a novel cardioprotective agent to be used pre CABG, to our knowledge; this is the first study of pretreatment Silymarin as cardioprotective agent in patients undergoing CABG.

2. Patients and methods

The local ethics committee approved the investigation, and informed written consent was obtained from all patients entering the study. 140 patients admitted to the hospital for the first time for elective coronary artery bypass surgery were invited to take part. They were randomized into three groups (G); G I: Administered Silymarin (Legalon® tablet), 140 mg×3; 1 day before surgery. G II: Administered Silymarin (Legalon® tablet), 140 mg×3; 3 days before surgery. G III: Control (no treatment). Patients receiving corticosteroids were deemed not eligible. Any drugs were withheld on the morning of surgery.

Surgical procedure: Specifications on the extracorporeal circulation circuit, cardiopulmonary bypass procedures and surgical procedures have been described previously [20].

At baseline, demographic data (age, sex, weight, BSA, BMI), and history of conventional vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking habit, alcohol abuse) were obtained.

Routine laboratory investigations were performed the first day after admission to the hospital after overnight fasting and later before discharged. It included levels of WBCs; differential counts (Neutrophils, Monocytes, Lymphocytes), RBCs, ESR, total cholesterol, LDL, vLDL, HDL, triglycerides, SGOT, SGPT, B.urea, S.creatinin, alkaline phosphatase, serum bilirubin, blood sugar, HbA1c, & ESR. Blood samples for troponin I (T), & creatine kinase; (CK-MB) measurement were obtained within 24 hours before surgery, & 2 hr, 24 hr post CABG. All laboratory tests were performed according to companys' procedures. Laboratory staffs were blind to the tested drug and groups.

Statistical analysis

The present Data was analyzed using Student 't' test, one-way analysis of covariance. $P < 0.05$ was considered to be significant. All data were analyzed using the statistical package SPSS (version 10.0) Continuous data are presented as mean ± SD and categorical data as absolute numbers, or mean.

3. Results

One hundred and forty patients [105 (75%) males, and 35 (25%) females] with a mean age of 64.5 years were included in the study. All underwent on-pump CABG.

No significant differences were noted between the groups in age, body surface area, BMI, and operation data. The demographic data on the 140 patients completing the study are presented

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in Table 1. Clinical & operative characteristics (Age, sex, body weight, smoking, left ventricular ejection fraction, usual administered drugs, other diseases, family history of coronary artery disease) were largely independent of silymarin treatment with no significance ($p>0.05$).

Variables	Silymarin (SM) Group (No. = 90)		Control Group (No. = 50)
	G I (n=40)	G II (n=50)	G III
Male/Female (No.)	68/22		37/13
Age (years) [a]	65		64
Body surface area (m^2) [b]	1.6 ± 0.2		1.7 ± 0.1
BMI (kg/m^2) [b]	42.3 ± 0.2		44.7 ± 0.2
Ejection fraction (%) [b]	58 ± 1		60 ± 1
Operative time (min) [b]	201 ± 16		200 ± 18
No. of grafts [a]	3		3.5
Hospitalization (days) [a]	4		7

Table 1. Clinical and Patients' data in Silymarin treated and control groups.

There was a significant decrease in post operative values of; WBCs counts, Neutrophil, monocytes, lymphocytes, RBCs, ESR (Figure1), total cholesterol, LDL, vLDL, & triglycerides (Figure2), SGOT, SGPT, alkaline phosphatase (47%), showed in (Figure 3), B.urea, S.creatinine, serum bilirubin (48%) (Figure 4), blood sugar, HbA1c in diabetic patients (43%) as showed in figure 5, in SM treated group compared to baseline and control group; (P=0.002), while there was an elevation of postoperative HDL values in patients treated with SM compared to control, (p=0.001).

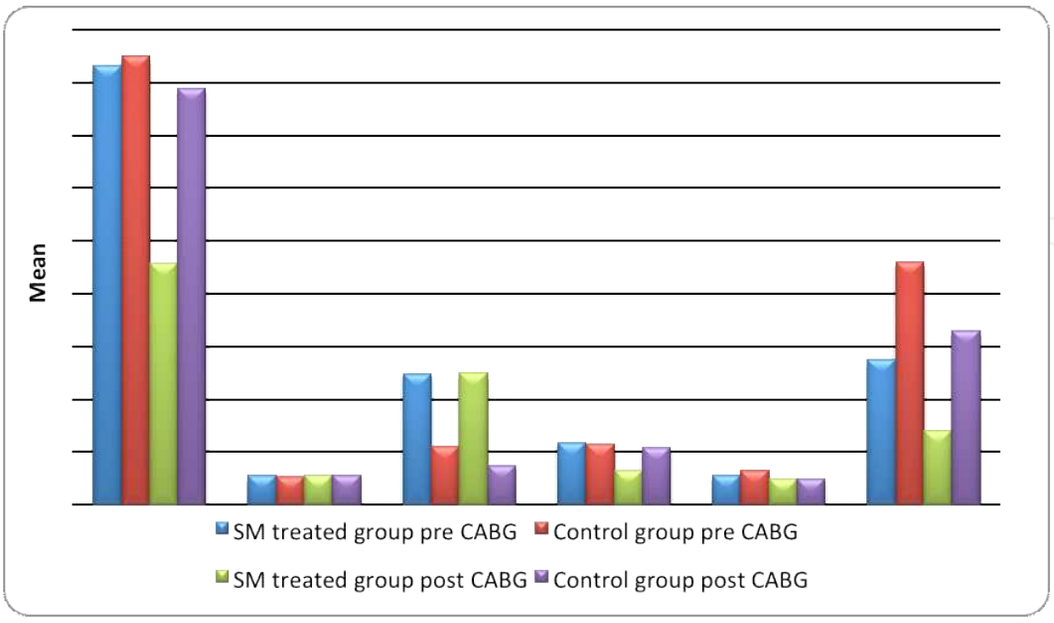

Figure 1. The mean values of Neutrophils, Monocytes, Lymphocytes, total WBCs, RBCs, and ESR for Silymarin treated and control groups pre and post CABG.

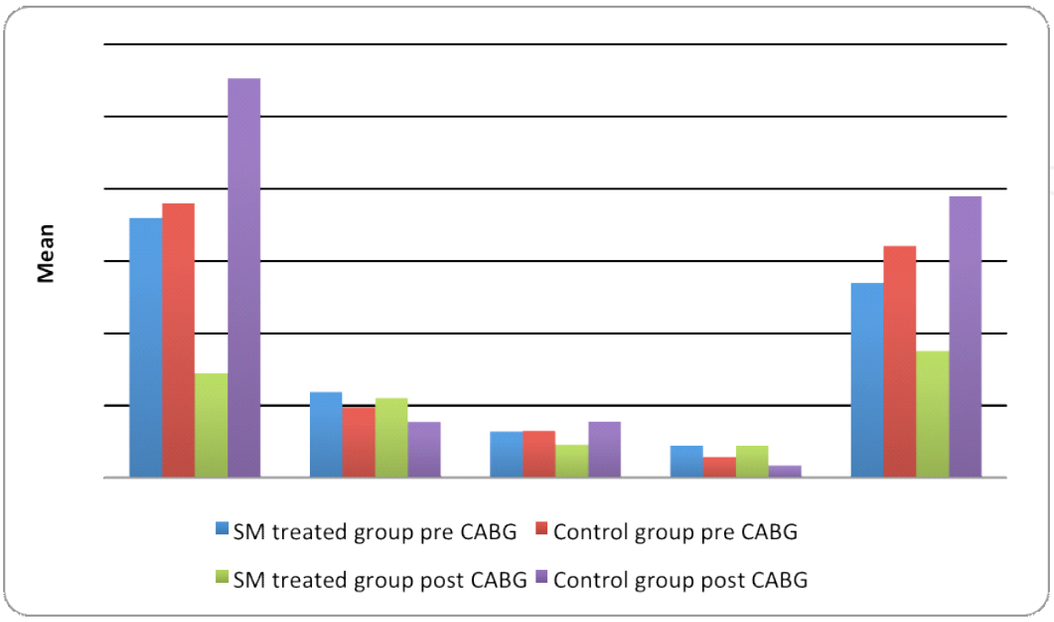

Figure 2. The mean values (mg/dL) of total cholesterol, LDL, vLDL, HDL, and triglycerides for Silymarin treated and control groups pre and post CABG.

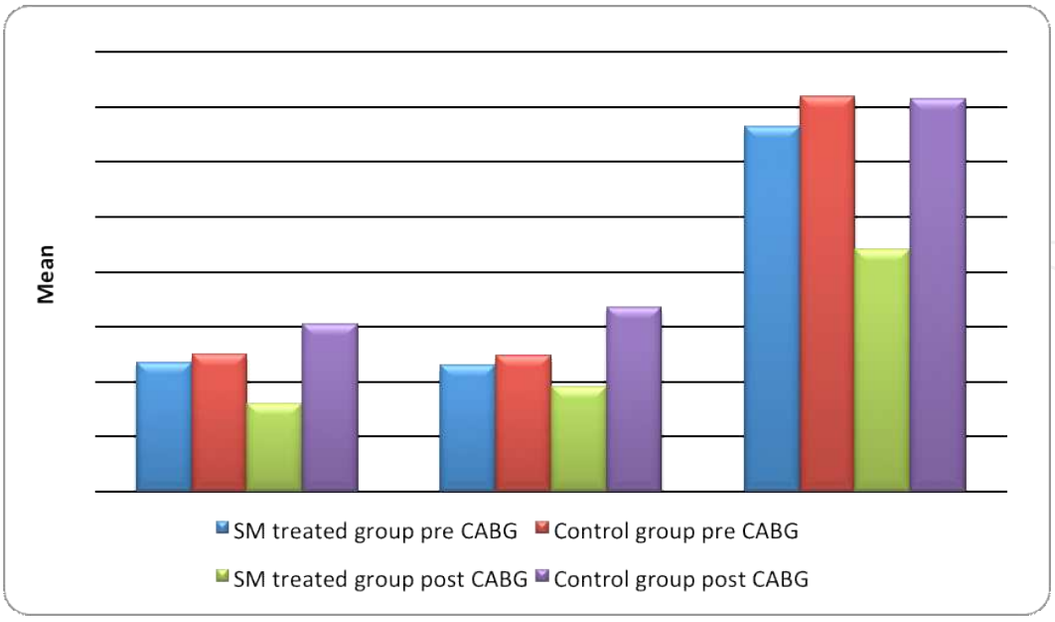

Figure 3. Mean values of SGOT, SGPT, & Alkaline phosphatase for both groups compared pre and post CABG.

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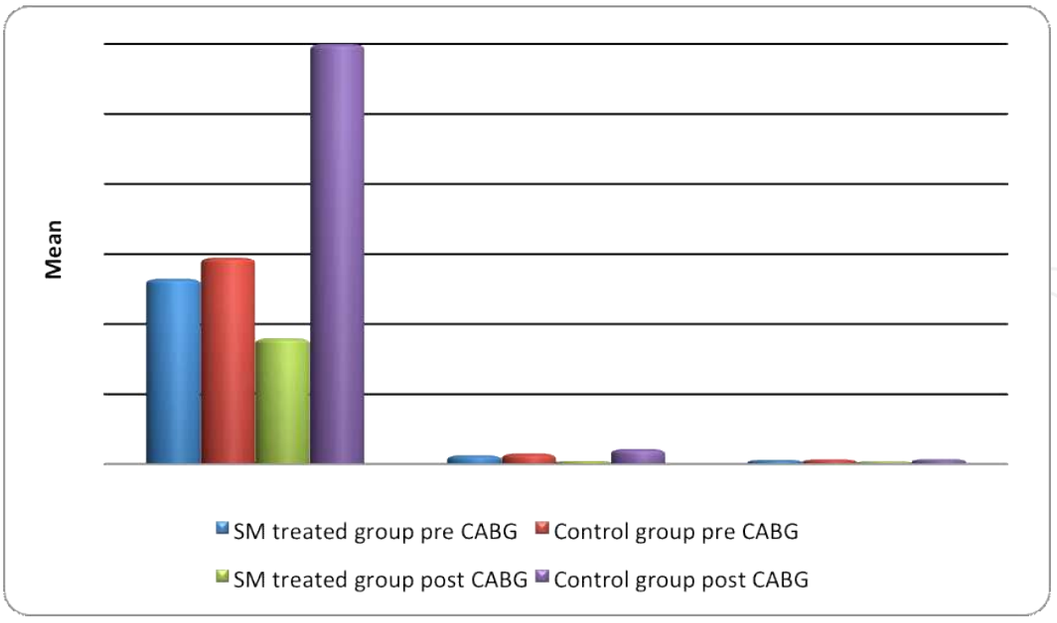

Figure 4. The mean values of blood urea & serum creatinin, & serum bilirubin in tested groups pre & post operation.

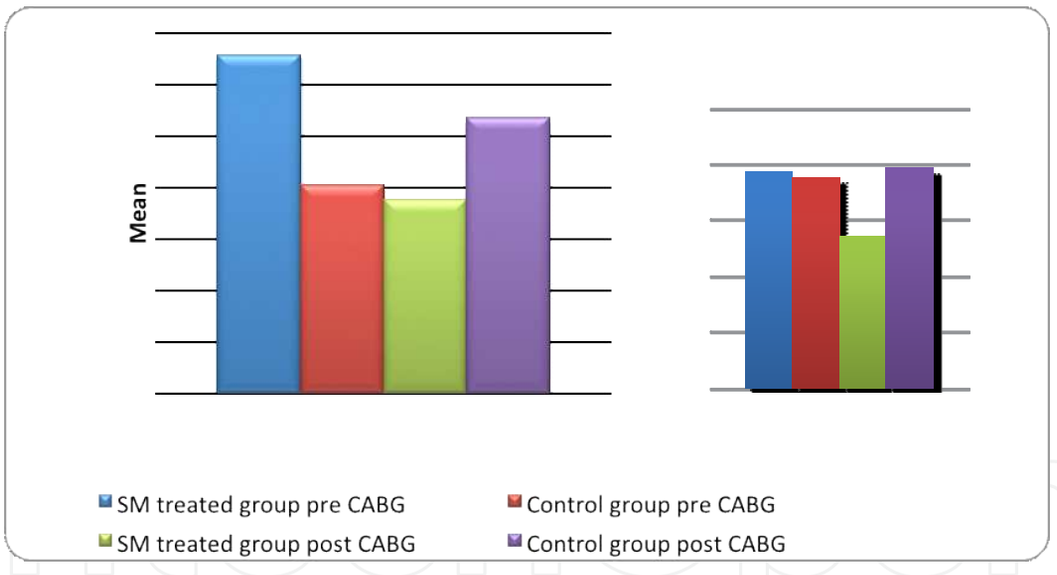

Figure 5. Mean values of fasting blood sugar, & glycosylated heamoglobin pre & post CABG for both groups.

Surgery was associated with a significant increase in troponin I (T1), CK-MB (CK1) in both groups, but after 24 hr post CABG there was a significant reduction of Troponin I (T2) values in SM treated group compared to baseline (T0), after 2 hour (T1), and control group, [p=0.001]. SM-treated patients released significantly less creatine kinase (CK)-MB than the control subjects postoperatively (CK1) after 2 hours, then back to normal levels after 24 hours (CK 2) [p = 0.004]; indicating less myocardial injury in patients receiving SM when compared to the control subjects (no significant change $p > 0.05$), as showed in figure 6.

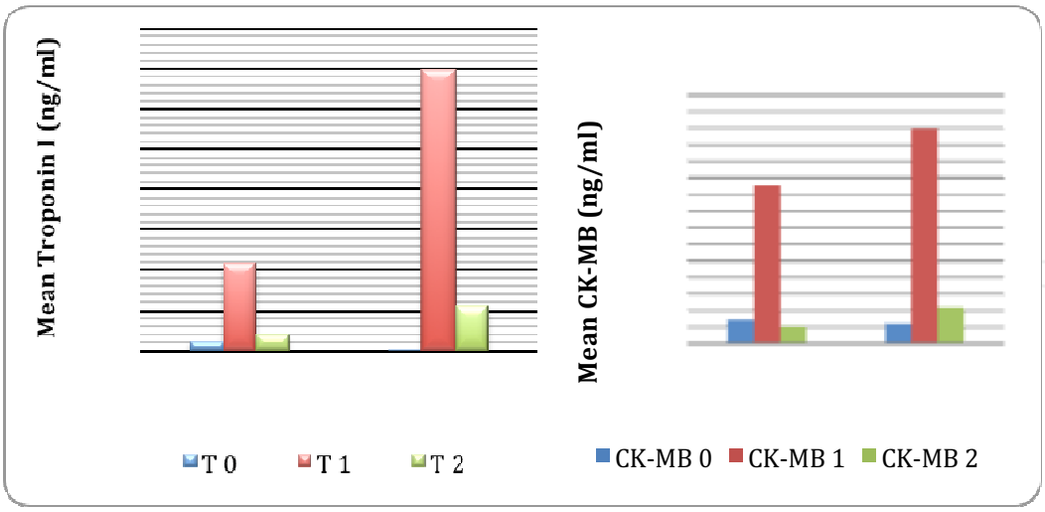

Figure 6. Mean Troponin I, & CK-MB values at different times in Silymarin (SM) treated patients and control groups. [T0=pre CABG, T1=2 hours after CABG, T2= 24 hours after CABG, CK-MB 0=pre CABG, CK-MB 1= 2 hours after CABG, CK-MB 2= 24 hours after CABG].

Patients treated with Silymarin before 3 days better than those treated before 1 day, but there was no statistical significant differences between them (G I & G II), $p>0.05$.

4. Discussion

Myocardial ischemia and reperfusion is a common occurrence in CABG patients. Reintroduction of oxygen to previously ischemic myocardium can result in irreversible tissue injury, and Ischemic myocardial damage is associated with inflammation [21, 22].

SM has been shown to have a potential positive effect on immune function by its ability to enhance neutrophil activity [23]. Silymarin & Silibinin by interacting with the lipid component of cell membranes can influence their chemical & physical properties. Studies in erythrocytes, mast cells, leucocytes, macrophages & hepatocytes have shown that SM renders cell membranes more resistant to lesions [24].

Studies have shown that silymarin exerts a number of effects, including inhibition of neutrophil migration [25, 24]. The inhibitory effects of silymarin on neutrophil function prevent post _ ischemic mucosal injury [26]. Activated neutrophils are thought to play a major role in ischemia-reperfusion injury [27]. This study agrees with that, SM treated groups showed a significant reduction of WBCs, neutrophils count post CABG, & ESR also. According to this, silymarin may prevent reperfusion injury so it may have a beneficial effect during CABG.

Milk thistle was able to inhibit the biosynthesis of cholesterol in the liver and reduce LDL cholesterol oxidation, one of the primary mechanisms of atherosclerosis [28,25]. This study agrees with it, SM treatment showed a significant reduction of total cholesterol, LDL, & vLDL, while HDL was elevated significantly.

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SM interact directly with the cell membrane components to prevent any abnormalities in the content of lipid fraction responsible for maintaining normal fluidity [29].

Silymarin appears to act as an antioxidant not only because it acts as a scavenger of the free radicals that induce lipid peroxidation, but also because it influences enzyme systems associated with glutathione & superoxide dismutase [30]. Also, prevent damage to rat heart membrane primarily through a free radical scavenging mechanism [31]. This study agrees with previous mentioned studies, the antioxidant activity of Silymarin prevents vascular endothelium injury during CABG.

In the present study, all patients showed significantly higher plasma levels of markers of perioperative myocardial tissue injury early after the start of reperfusion. Silymarin treated group showed a significant reduction of all measured parameters compared to baseline and control.

Alkaline phosphatase, & serum bilirubin was elevated preoperatively in 47%, and 48% of enrolled patients, respectively, pretreatment with Silymarin showed a significant reduction post operatively because SM have the ability to prevent injury from different causes.

Blood sugar & HbA1c in diabetic patients (43%) were diminished significantly in those treated by SM.

SM counteracted the increase in the cardiac enzymes and cTnI concentration induced by cisplatin, toward near normal levels. Rao and Viswanath 2007 [19] reported that the administration of SM before ischemia–reperfusion-induced myocardial infarction maintained the levels of marker enzymes (LDH, CK and CK-MB) compared to isoproterenol-injected rats. A possible explanation is that silymarin, via its anti-lipid peroxidation activity, causes stabilization of cardiac membranes and prevents the leakage of cardiac enzymes [32]. Silibinin induced cardiac myocyte expression of Bcl-2 protein, which prevented permeability transition pore opening, and, therefore, cytochrome c release decreased. These events might be one of the mechanisms of silymarin-mediated stabilization of the mitochondrial membrane [33]. This study agrees with the above study in which Troponin I, and CK-MB diminished significantly in SM treated group compared to baseline and control.

The anti-inflammatory activity (significant reduction of cytokines post operatively), & antioxidant effects of SM during CABG [20], in addition to that, the highly significant reduction in serum levels of troponin I, & CK-MB, confirm the cardioprotection activity of SM during CABG. This mechanism of action may reduce ischemia-reperfusion injury, and protect the myocardium.

The results of this study indicate that SM pretreatment induces potent endogenous protection against subsequent ischemic stress in the human myocardium, and reduced the damage caused by reperfusion injury. SM has the ability to regulate membrane permeability and to increase membrane stability in the presence of xenobiotic damage, capacity to regulate nuclear expression by means of a steroid-like effect.

There was no statistically significant difference between the two treated groups, even the results of patients treated with SM before 3 days better than those treated before 1 day of CABG surgery. The data of this study needs further large-scale, randomized, double blind technique studies for other cardiovascular diseases to confirm the present study before clinical use of Silymarin.

5. Conclusion

The authors conclude that CABG surgery need using cardioprotective agent pre operation and suggest using other pharmaceutical preparation I.V. dosage form of SM and studying the pharmacokinetics during CABG surgery. The pre-operative administration of Silymarin may reduce perioperative morbidity and myocardial injury during CABG surgery. The authors suggest a large-scale, randomized, double blind study with cardiovascular events before Silymarin could be considered for clinical use.

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