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Silymarin for the Prevention of Contrast-Induced Nephropathy after Percutaneous Coronary Intervention in Patients with Acute ST-Segment Elevation Myocardial Infarction

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ABSTRACT

Background: Contrast-induced nephropathy (CIN) is a serious complication of angiographic procedures, increasing morbidity and mortality. Oxidative stress and inflammation play key roles in its pathogenesis. Silymarin, a flavonoid complex with antioxidant and anti-inflammatory properties, may offer renal protection.

Objective: To assess the protective effect of a single dose of silymarin against CIN in patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

Patients and Methods: In this prospective interventional study, 200 STEMI patients undergoing PPCI were randomized into two equal groups. The study group received 140 mg of silymarin alongside standard dual antiplatelet therapy, while the control group received standard therapy alone. Renal function was assessed at baseline and post-procedure using serum creatinine and estimated glomerular filtration rate (eGFR). CIN was defined as a ≥25% increase in serum creatinine or an absolute rise of ≥0.5 mg/dL within 48–72 hours post-contrast exposure.

Results: CIN incidence was significantly lower in the silymarin group (12.0% vs. 28.0%, $p = 0.005$). Post-procedural serum creatinine increase was smaller (ΔS. Creat: 0.18 ± 0.28 vs. 0.35 ± 0.42 mg/dL, $p = 0.011$), with a lesser eGFR reduction (ΔGFR: -8.63 ± 17.43 vs. -18.21 ± 23.95 mL/min, $p < 0.001$). Contrast volume and procedural duration were higher in the study group ($p < 0.001$, $p = 0.003$).

Conclusion: A single dose of silymarin significantly reduced CIN incidence in STEMI patients undergoing PPCI, highlighting its potential nephroprotective effect in high-risk populations.

Keywords: Silymarin, Contrast-Induced Nephropathy, ST-Elevation Myocardial Infarction, Percutaneous Coronary Intervention, Nephroprotection.

INTRODUCTION

Contrast-induced nephropathy (CIN) is a critical adverse event associated with angiographic procedures, manifesting as renal dysfunction, which is defined by a ≥25% elevation in serum creatinine from baseline or an absolute increase of ≥0.5 mg/dL within 48–72 hours following intravascular contrast administration [1].

The precise mechanisms contributing to CIN remain incompletely elucidated, though they appear to be multifactorial. Intrinsic factors, such as oxidative stress, localized hypoxia, and the direct cytotoxic impact of contrast agents, interplay with extrinsic influences, including dehydration and diminished intravascular volume [2].

The occurrence of CIN is influenced by multiple determinants, including the contrast agent's type and volume, as well as patient comorbidities. Its prevalence varies from approximately 2% in individuals without risk factors to as high as 34% in those classified as high risk [3]. Given the substantial health burden linked to CIN, proactive preventive measures are essential to decrease its occurrence and alleviate its consequences [4].

Silymarin, obtained from Silybum marianum, also known as milk thistle, has been historically employed as a therapeutic agent for liver-related disorders [5]. Silymarin, an extract derived from the seeds of this plant, consists of silydianin, silybin, and silychristin. This flavonoid complex exhibits strong antioxidant and anti-inflammatory properties. Research has highlighted its therapeutic efficacy in mitigating chemically induced diabetic nephropathy and nephrotoxicity. Given the pivotal role of oxidative stress and inflammation in CIN pathogenesis, silymarin emerges as a promising agent for its prevention [6].

This study aimed to assess the potential protective effect of a single dose of silymarin in mitigating CIN in patients diagnosed with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

PATIENTS AND METHODS

Study Design and Participants

This interventional study included 200 patients with acute STEMI referred for PPCI at the Cardiology Department, Ain Shams University Hospitals, Cairo, Egypt.

Prior to the intervention, patients in the emergency room (ER) were stratified into two groups. **The study group,** comprising 100 patients, received 300 mg of aspirin, 600 mg of clopidogrel, and a single dose of 140 mg of silymarin, whereas **the control group,** also consisting of 100 patients, was administered 300 mg of aspirin and 600 mg of clopidogrel alone.

Eligibility Criteria:

Patients were excluded if they had an allergy to contrast media, were asymptomatic for 24 hours or more, had received streptokinase, experienced

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mechanical complications, had undergone coronary artery bypass grafting (CABG) or valve replacement, refused to undergo PCI, or had contraindications to silymarin (reported in less than 1% of cases as causing an allergic reaction).

All patients were subjected to the following

Full history: Personal history, and a detailed risk profile for hypertension, diabetes mellitus, smoking status and dyslipidemia. Past history included previous acute myocardial infarction (AMI), anginal symptoms, or renal impairment. Family history assessed premature coronary artery disease (CAD) (men <55 years, women <65 years) and sudden cardiac death. Evaluation of presenting complaints focused on the qualitative aspects of chest pain, its duration before hospitalization, coexisting symptoms, and angina-equivalent indicators.

Full clinical examination: A thorough general assessment was performed, with special emphasis on vital signs. **A detailed local cardiac examination** was conducted to evaluate mechanical complications and indicators of heart failure, including ventricular septal defects, S3 gallop, mitral regurgitation, and basal rales.

Baseline estimated creatinine clearance and serum creatinine levels were assessed immediately prior to admission and re-evaluated 48 hours post-contrast media administration. Creatinine clearance was calculated using the Cockcroft-Gault equation: [(140 − age in years) × weight in kg] / 72 × serum creatinine in mg/dL. For females, the result was multiplied by 0.8 [7].

Twelve-lead surface ECG

A standard 12-lead ECG was performed for all patients upon admission using an ECG machine set at a paper speed of 25 mm/s and a gain of 10 mm/mV. ST-segment and T-wave changes suggestive of acute myocardial ischemia were assessed. New or presumed new J-point elevation of ≥1 mm in all leads except V2 and V3 was considered an ischemic response. In healthy men under 40, J-point elevation in leads V2 and V3 could reach up to 2.5 mm, decreasing with age. Sex-based differences necessitated distinct cutoff points, and ST-segment shifts were required in at least two contiguous leads [8].

Echocardiography Assessment

Echocardiographic assessment was performed for each patient after primary PCI to evaluate ejection fraction (EF), left ventricular (LV) dimensions, segmental wall motion abnormalities, and severe valvular abnormalities. EF was measured using the Simpson method, which involves tracing the LV endocardial border in both apical four-chamber and two-chamber views during end-systole and end-diastole. Endorsed by the American Society of Echocardiography, this technique segments the LV cavity into a predefined series of disks, typically numbering 20, with volume estimations derived from these delineations [9]. LVEF (%) reference values in males: normal (52–72%), mildly abnormal (41–51%), moderately abnormal (30–40%), and severely abnormal (<30%).

In adherence to clinical standards, angiography was performed by experienced interventional cardiologists using either the transfemoral or transradial technique. A nonionic, iso-osmolar contrast agent was employed in all cases, and key procedural metrics, such as total contrast dose, procedure duration, and fluoroscopy time, were systematically documented.

Ethical considerations:

Upon receiving approval from the Research Ethics Committee of Ain Shams University, the study commenced. All the participants were fully briefed on the study details and provided written consent before enrollment, with the consent form explicitly detailing their authorization for participation and data publication while safeguarding confidentiality and privacy. The study adhered to the ethical guidelines established in the Declaration of Helsinki by the World Medical Association for human research.

Data Management:

Data were collected, categorized, reviewed, and entered using the Statistical Package for the Social Sciences (IBM SPSS) version 20. Quantitative variables following a parametric distribution were represented as mean, standard deviation, and range, and as median and range if they were nonparametric, while qualitative data were expressed as frequencies and percentages. Chi-square test was employed to compare qualitative variables between two groups. For quantitative data with a parametric distribution, comparisons between two groups were performed using the independent t-test. A 5% margin of error was established, corresponding to a 95% confidence interval. Statistical significance was defined as $p < 0.05$.

RESULTS

The baseline characteristics of the control and study groups were comparable, with no significant differences observed in age, gender, diabetes, hypertension, weight, height, BMI, random blood sugar (RBS), Mehran score, systolic blood pressure (SBP), and heart rate. However, renal impairment/chronic kidney disease (RI/CKD) was significantly more prevalent in the study group. The study group also had significantly higher baseline serum creatinine levels and lower baseline glomerular filtration rate (GFR). Additionally, LVEF was markedly elevated in study group. Diastolic blood pressure (DBP) was slightly lower in the study group **(Table 1)**.

Table 1: Comparison between the Control and Study Groups Regarding Baseline Demographics, Anthropometric Measures, Clinical Characteristics, Vital Data, Laboratory Results, and Echocardiographic Findings

Variable	Control Group (n=100)	Study Group (n=100)	p-value
Age (years)	58.36 ± 12.01	61.14 ± 11.66	0.098
Gender (Male)	75 (75.0%)	76 (76.0%)	0.869
HF symptoms	15 (15.0%)	19 (19.0%)	0.451
RI/CKD (Scr > 1.4 mg/dl)	22 (22.0%)	38 (38.0%)	0.014*
Diabetic	45 (45.0%)	41 (41.0%)	0.568
Hypertensive	60 (60.0%)	58 (58.0%)	0.774
Weight (kg)	84.03 ± 15.47	81.99 ± 12.41	0.305
Height (cm)	171.86 ± 7.90	170.32 ± 7.22	0.152
BMI (kg/m²)	28.54 ± 5.42	28.26 ± 3.85	0.676
RBS (mg/dL)	226.33 ± 42.05	216.85 ± 10.77	0.587
S. Creat (mg/dL) baseline	1.07 ± 0.2	1.25 ± 0.2	0.004*
Baseline GFR (mL/min)	95.33 ± 36.19	79.09 ± 32.08	0.001*
Mehran Score	4 (1 - 5)	3 (0 - 5)	0.227
LVEF (%)	40.00 ± 9.17	46.13 ± 11.63	<0.001*
Systolic BP (mmHg)	133.10 ± 26.62	128.20 ± 25.20	0.183
Diastolic BP (mmHg)	81.28 ± 14.82	77.07 ± 14.58	0.044
Heart rate (bpm)	82.04 ± 16.14	80.61 ± 11.64	0.473

Date were presented as Mean ± SD, n (%), Median (Range), HF: Heart Failure, RI/CKD: Renal Impairment/Chronic Kidney Disease, Scr: Serum Creatinine, RBS: Random Blood Sugar, S. Creat: Serum Creatinine, GFR: Glomerular Filtration Rate, LVEF: Left Ventricular Ejection Fraction, BMI: Body Mass Index, BP: Blood Pressure, bpm: Beats per Minute, *: Statistically Significant p-value as $p<0.05$.

The study group had a significantly longer procedural time and higher contrast volume usage compared to the control group. However, fluoroscopy time was notably reduced in study group. Post-PCI serum creatinine levels and GFR were comparable between the groups. The study group exhibited a significantly lower increase in serum creatinine and less reduction in GFR. Additionally, a significant reduction in CIN incidence was noted in the study group **(Table 2)**.

Table 2: Comparison between the Control and Study Groups Regarding Procedural Characteristics, Post-PCI Renal Function Changes, and Incidence of CIN

Variable	Control Group (n=100)	Study Group (n=100)	P-value
Whole time (min)	58.16 ± 16.42	66.19 ± 20.98	0.003*
Contrast volume (ml)	93.01 ± 38.40	146.76 ± 69.14	<0.001*
Fluoro Time (min)	40.07 ± 12.39	35.14 ± 10.18	0.002*
Post PCI S. Creat (mg/dL)	1.41 ± 0.67	1.43 ± 0.58	0.821
Post PCI GFR (ml/min)	77.11 ± 36.54	70.45 ± 31.17	0.167
S. Creat Δ change	0.35 ± 0.42	0.18 ± 0.28	0.011*
GFR Δ change	-18.21 ± 23.95	-8.63 ± 17.43	<0.001*
CIN (Positive)	28 (28.0%)	12 (12.0%)	0.005*

Data were presented as Mean ± SD, n (%), *: Statistically Significant p-value as $p<0.05$, PCI: Percutaneous Coronary Intervention, S. Creat: Serum Creatinine, GFR: Glomerular Filtration Rate, CIN: Contrast-Induced Nephropathy, Fluoro Time: Fluoroscopy Time.

A significant age difference was observed, with CIN-positive patients being older than their CIN-negative counterparts. CIN was more prevalent in patients with heart failure symptoms, renal impairment, diabetes mellitus, and hypertension. Procedural factors, including contrast volume, were significantly higher in the CIN group, while procedural and fluoroscopy times were comparable. Baseline renal function was worse in the CIN group, with higher pre-PCI serum creatinine and lower GFR. Post-PCI renal deterioration was more pronounced in the CIN group, with a greater increase in serum creatinine and a larger decrease in GFR. The Mehran risk score was significantly higher in CIN patients, and LVEF was lower **(Table 3)**.

Table 3: Comparison of Patients with and without CIN Regarding Baseline Characteristics, Clinical and Laboratory Parameters, Procedural Data, and Post-PCI Outcomes

Variable	Patients Without CIN (n=160)	Patients With CIN (n=40)	P-value
Age (years)	58.74 ± 11.21	63.78 ± 13.74	0.016*
Gender (Male)	122 (76.3%)	29 (72.5%)	0.622
Weight (kg)	82.58 ± 13.14	84.73 ± 17.20	0.389
Height (cm)	171.13 ± 7.77	170.93 ± 6.92	0.878
BMI (kg/m²)	28.26 ± 4.46	28.98 ± 5.54	0.385
HF Symptoms (Positive)	23 (14.4%)	11 (27.5%)	0.048*
RI/CKD (Positive)	40 (25.0%)	20 (50.0%)	0.002*
Diabetes Mellitus (Positive)	61 (38.1%)	25 (62.5%)	0.005*
Hypertension (Positive)	88 (55.0%)	30 (75.0%)	0.021*
Systolic BP (mmHg)	129.50 ± 25.37	135.25 ± 28.10	0.211
Diastolic BP (mmHg)	78.85 ± 14.49	80.48 ± 16.18	0.536
HR (bpm)	80.42 ± 13.54	84.95 ± 15.59	0.068
Random Blood Sugar (mg/dL)	204.39 ± 105.35	290.38 ± 160.62	<0.001*
Serum Creatinine Before PCI (mg/dL)	1.11 ± 0.42	1.34 ± 0.51	0.005*
GFR Before PCI (mL/min)	90.40 ± 34.46	74.45 ± 35.01	0.010*
Mehran Score (Median, IQR)	2 (0 - 5)	5 (4 - 9)	<0.001*
Procedure Time (min)	61.61 ± 19.59	64.43 ± 17.69	0.409
Contrast Volume (mL)	112.09 ± 54.13	151.05 ± 79.93	<0.001*
Fluoro Time (min)	36.84 ± 11.08	40.68 ± 13.09	0.061
LVEF (%)	44.09 ± 10.92	38.95 ± 9.86	0.007*
Post PCI S. Creat (mg/dL)	1.23 ± 0.15	2.19 ± 0.23	<0.001*
Post PCI GFR (mL/min)	81.59 ± 32.71	42.56 ± 17.37	<0.001*
Creatinine Δ Change	0.12 ± 0.17	0.86 ± 0.32	<0.001*
GFR Δ Change	-8.81 ± 18.91	-31.88 ± 21.24	<0.001*

Data were presented as Mean ± SD, n (%), Median (Range), HF: Heart Failure, RI/CKD: Renal Impairment/Chronic Kidney Disease, S. Creat: Serum Creatinine, GFR: Glomerular Filtration Rate, BMI: Body Mass Index, Fluoro Time: Fluoroscopy Time, LVEF: Left Ventricular Ejection Fraction, BP: Blood Pressure, bpm: Beats per Minute, *: Statistically Significant p-value as $p<0.05$.

Univariate logistic regression analysis identified several significant predictors of CIN, including age >75 years, renal impairment, diabetes mellitus, random blood sugar >200 mg/dL, serum creatinine >1.4 mg/dL, baseline GFR ≤55.59 mL/min, Mehran score >3, contrast volume >90 mL, and LVEF ≤35%. However, in multivariate analysis, only contrast volume >90 mL and LVEF ≤35% remained independent predictors of CIN, while other factors lost statistical significance **(Table 4)**.

Table 4: Univariate and Multivariate Logistic Regression Analysis for Predictors of Occurrence of CIN

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR Lower	Upper	P-value	Odds ratio (OR)	95% C.I. for OR Lower	Upper
Age>75	0.001*	4.333	1.872	10.031	0.120	2.335	0.801	6.805
HF symptoms	0.052	2.259	0.992	5.143	0.930	1.048	0.365	3.012
Renal impairment	0.003*	3.000	1.467	6.137	0.381	0.344	0.032	3.752
Diabetes mellitus	0.006*	2.705	1.323	5.531	0.523	1.588	0.384	6.575
Hypertensive	0.024	2.455	1.125	5.357	0.484	1.388	0.554	3.478
Random blood sugar (>200mg\dl)	0.001*	3.429	1.673	7.030	0.707	1.308	0.324	5.283
S. Creatinine (>1.4mg\dl)	0.001*	3.326	1.628	6.793	0.195	4.895	0.443	54.047
GFR before PCI ≤55.59 (ml/min)	<0.001*	4.636	2.143	10.030	0.205	2.160	0.656	7.110
Mehran Score>3	<0.001*	5.167	2.306	11.576	0.574	1.377	0.451	4.205
Contrast volume >90ml	<0.001*	5.257	2.092	13.213	0.002*	5.990	1.971	18.198
Fluoro Time (>36min)	0.092	1.842	0.904	3.752	0.625	0.798	0.323	1.970
LVEF≤35	0.002*	3.029	1.488	6.166	0.031*	2.512	1.085	5.817

CIN: Contrast-Induced Nephropathy, OR: Odds Ratio, C.I.: Confidence Interval, HF: Heart Failure, S. Creatinine: Serum Creatinine, GFR: Glomerular Filtration Rate, PCI: Percutaneous Coronary Intervention, Fluoro Time: Fluoroscopy Time, LVEF: Left Ventricular Ejection Fraction.

DISCUSSION

Prospective studies have documented a broad range of CIN incidence, from absent cases to as high as 50%, primarily due to variations in baseline creatinine levels, pre-existing comorbidities, and other contributory factors of acute kidney injury [10]. CIN incidences of 3.3% and 16.5% were documented in two large-scale investigations [11,12]. The underlying mechanisms of CIN are multifactorial, encompassing a reduction in nephronal antioxidant capacity alongside the direct cytotoxic actions of contrast media on renal cells [13]. The current study aimed to evaluate the protective role of silymarin against CIN.

No statistically significant variation was noted between the study and control groups in terms of demographic parameters, including age, gender, weight, height, and body mass index. These results correspond with those of **Sedighifard *et al.*** [14], who conducted a placebo-controlled clinical trial on 143 patients with chronic stable angina undergoing elective coronary angiography. Their study, which randomized low- to moderate-risk CIN patients to receive either silymarin (280 mg) or a placebo two hours before contrast administration, further substantiates the comparability of baseline characteristics.

There was a difference in the silymarin dose between the current study and the trial by **Sedighifard *et al.*** [14]. In our study, patients received a single 140 mg dose immediately before the intervention, whereas their trial administered 280 mg.

Regarding clinical characteristics, no statistically significant differences were observed between the control and study groups in terms of heart failure symptoms, diabetes mellitus, hypertension, random blood sugar, SBP, Mehran score and heart rate. However, baseline serum creatinine was higher in the study group compared to the control group. This contrasts with the findings of **Sedighifard *et al.*** [14], where the placebo group had a higher baseline creatinine level than the silymarin group.

Baseline GFR was elevated in control group when compared to study group, which contrasts with the findings of **Sedighifard *et al.*** [2], where the control group had a lower baseline GFR (74.3 ± 11.2 mL/min) than the silymarin group (83.7 ± 13.7 mL/min). In our study, we used estimated GFR (eGFR) as it is considered a more accurate measure of renal function than serum creatinine alone, a methodology initially introduced by **Gruberg *et al.*** [14].

Regarding procedural data, there was a statistically significant difference between the control and study groups in the total procedure time. Both low-osmolar and iso-osmolar contrast agents were utilized, with the study group receiving a notably greater contrast volume in comparison to control group. At this point, both baseline serum creatinine and contrast media volume were higher in the study group than in the control group, which may have influenced renal function outcomes.

With respect to procedural parameters, contrast volume was the sole factor that demonstrated a significant increase in CIN group relative to the no-CIN group. Therefore, restricting contrast dose is recommended, as each additional 100 mL of contrast has been associated with a 12% increase in the risk of CIN [12].

There is broad consensus that high-osmolar contrast media should be avoided, especially in patients at elevated risk for CIN. However, ongoing discourse persists regarding whether iso-osmolar contrast agents offer superior safety compared to low-osmolar contrast media in this high-risk population [16-17]. Regarding contrast volume, a relatively safe range is considered to be between 70–220 mL, while volumes exceeding 300 mL are recognized as a significant predictor of CIN [12,18].

This single-center study may limit generalizability. The sample size, though adequate, may not detect rare adverse effects. Residual confounding is possible despite adjustments. Only a single silymarin dose was assessed, and long-term renal outcomes were not evaluated. Further investigations incorporating larger study populations and long-term follow-up are warranted.

CONCLUSIONS

A single dose of silymarin significantly reduced the incidence of CIN in STEMI patients undergoing PPCI, suggesting its potential as a nephroprotective agent in high-risk populations. Further large-scale studies are warranted to confirm these findings.

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