Effects of Curcuminoids on Frequency of Acute Myocardial Infarction After Coronary Artery Bypass Grafting

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It is well established that myocardial infarction (MI) associated with coronary artery bypass grafting (CABG) predicts a poor outcome. Nevertheless, cardioprotective therapies to limit myocardial injury after CABG are lacking. Previous studies have shown that curcuminoids decrease proinflammatory cytokines during cardiopulmonary bypass surgery and decrease the occurrence of cardiomyocytic apoptosis after cardiac ischemia/reperfusion injury in animal models. We aimed to evaluate whether curcuminoids prevent MI after CABG compared to placebo. The 121 consecutive patients undergoing CABG were randomly allocated to receive placebo or curcuminoids 4 g/day beginning 3 days before the scheduled surgery and continued until 5 days after surgery. The primary end point was incidence of in-hospital MI. The secondary end point was the effect of curcuminoids on C-reactive protein, plasma malondialdehyde, and N-terminal pro–B-type natriuretic peptide levels. Baseline characteristics were comparable between the curcuminoid and placebo groups. Mean age was 61 ± 9 years. On-pump CABG procedures were performed in 51.2% of patients. Incidence of in-hospital MI was decreased from 30.0% in the placebo group to 13.1% in the curcuminoid group (adjusted hazard ratio 0.35, 0.13 to 0.95, p = 0.038). Postoperative C-reactive protein, malondialdehyde, and N-terminal pro–B-type natriuretic peptide levels were also lower in the curcuminoid than in the placebo group. In conclusion, we demonstrated that curcuminoids significantly decreased MI associated with CABG. The antioxidant and anti-inflammatory effects of curcuminoids may account for their cardioprotective effects shown in this study. (Am J Cardiol 2012;110:40–44)

Curcuminoids, the polyphenols responsible for the yellow color of the curry spice turmeric, have been used to treat a variety of diseases in traditional Chinese and Indian medicine. The major curcuminoids present in turmeric are curcumin (curcumin I), demethoxycurcumin (curcumin II), and bisdemethoxycurcumin (curcumin III).[1] Modern scientific research has confirmed the good therapeutic effects of the curcuminoid complex and its pharmacologic safety has been well established.[2] A previous study has shown that curcuminoids suppress proinflammatory cytokines during cardiopulmonary bypass surgery and decrease the occurrence of cardiomyocytic apoptosis after cardiac ischemia/reperfusion injury in an animal model.[3] Furthermore, a histopathologic study has demonstrated that curcuminoid treatment decreases the degree of myocardial necrosis in isoproterenol-administered rats.[4] The well-known anti-inflammatory, antioxidant, and membrane-stabilizing effects of curcuminoids may help preserve cellular viability during cardiopulmonary bypass surgery.[5,6] Therefore, curcuminoids may have a potential role in the limitation of myocardial ischemia/reperfusion injury after coronary artery bypass grafting (CABG). The present study evaluated whether curcuminoids prevent myocardial infarction (MI) after CABG compared to placebo.

Methods

The present study was a randomized, prospective, double-blinded, placebo-controlled trial performed at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University. We prospectively studied 121 consecutive patients undergoing CABG without valve surgery from September 2009 to December 2011. Informed consent was obtained from each patient to participate in the study. Patients were excluded if they had emergency cardiac surgery or any increase in creatine kinase-MB above the upper limit of the normal range at time of randomization. Because curcuminoids are mainly metabolized by the liver, patients with cholesteric jaundice (total bilirubin higher than twofold the upper normal limit) or severe liver disease (aspartate aminotransferase or alanine amino-

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This work was supported by Grants MRG 5380258 (Dr. Wongcharoen), MRG 5280169 (Dr. Phrommintikul), and RTA5280006 (Dr. Chattipakorn) from the Thailand Research Fund, Bangkok, Thailand; The Research and Development Institute, the Government Pharmaceutical Organization, Bangkok, Thailand (Dr. Wongcharoen); and the Faculty of Medicine Endowment Fund for Medical Research, Chiang Mai University, Chang Mai, Thailand (Dr. Wongcharoen, Dr. Phrommintikul, and Dr. Chattipakorn).

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0002-9149/12/$ – see front matter
doi:10.1016/j.amjcard.2012.02.043

Table 1
Demographic data and clinical features

Characteristics	Curcuminoid (n = 61)	Placebo (n = 60)	p Value
Age (years)	61.0 ± 9.1	61.1 ± 8.2	0.966
Men	34 (55.7%)	35 (58.3%)	0.917
Body mass index (kg/m^2)	24.1 ± 3.4	24.8 ± 4.8	0.290
New York Heart Association class	1.9 ± 0.5	2.0 ± 0.5	0.224
Canadian Cardiovascular Society class	1.9 ± 0.6	2.0 ± 0.5	0.194
Serum creatinine (mg/dl)	1.3 ± 0.4	1.4 ± 0.6	0.380
Preoperative creatine kinase-MB (ng/ml)	4.5 ± 4.1	5.5 ± 6.8	0.308
Preoperative C-reactive protein (mg/dl)	0.4 ± 0.5	0.5 ± 0.9	0.313
Preoperative malondialdehyde (mmol/ml)	7.4 ± 1.4	7.4 ± 1.1	0.908
Preoperative N-terminal pro–B-type natriuretic peptide (pg/ml)*	410.9 ± 577.2	533.4 ± 1,529.7	0.219
Diabetes mellitus	23 (37.7%)	30 (50.0%)	0.238
Hypertension†	55 (90.2%)	54 (90.0%)	1.000
Dyslipidemia‡	55 (90.2%)	52 (86.7%)	0.751
Previous myocardial infarction	17 (27.9%)	15 (25.0%)	0.879
Current smoker	8 (13.1%)	4 (6.7%)	0.378
Heart failure	5 (8.3%)	6 (10.0%)	1.000
Previous coronary angioplasty	4 (6.6%)	1 (1.7%)	0.371
Left ventricular ejection fraction (%)	54.8 ± 14.4	51.6 ± 15.1	0.483
Preoperative medications			
Aspirin or clopidogrel	55 (90.2%)	59 (98.3%)	0.125
β blocker	48 (78.7%)	48 (80.0%)	0.891
Statin	56 (91.8%)	56 (93.3%)	1.000
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	42 (68.9%)	44 (73.3%)	0.732

* Median ± interquartile range.
† Blood pressure ≥140/90 mm Hg or currently treated with antihypertensive drugs.
‡ Low-density lipoprotein cholesterol >100 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, or triglyceride >150 mg/dl.

Table 2
Perioperative features of patients in curcuminoid and placebo groups

Characteristics	Curcuminoid (n = 61)	Placebo (n = 60)	p Value
Vessel involvement			
Left main coronary artery stenosis	12 (20.3%)	17 (28.3%)	0.422
3-Vessel disease	45 (76.3%)	49 (81.7%)	0.619
Off-pump coronary artery bypass grafting	32 (52.5%)	27 (45.0%)	0.523
On-pump coronary artery bypass grafting	29 (47.5%)	33 (55.0%)	
On-pump with beating heart	14 (23.3%)	17 (28.3%)	
On-pump with cardioplegic arrest	15 (24.6%)	16 (26.7%)	
Cardiopulmonary bypass duration (minutes)	108.5 ± 48.1	106.6 ± 43.0	0.872
Cross-clamp duration (minutes)	80.0 ± 27.7	71.4 ± 26.3	0.379
Temporary ventricular pacing	24 (39.3%)	19 (31.8%)	0.231
Number of bypass grafts	3.5 ± 1.3	3.7 ± 1.0	0.374
Myocardial infarction after coronary artery bypass grafting	8 (13.1%)	18 (30.0%)	0.028
Non–Q-wave myocardial infarction	8 (13.1%)	15 (25.0%)	
Q-wave myocardial infarction	0 (0%)	3 (5.0%)	

transferase higher than threefold the upper normal limit) were not included in the study.

Curcuminoids and placebo used in the present study were provided in caplet form by the Research and Development Institute, the Government Pharmaceutical Organization, Bangkok, Thailand. One curcuminoid capsule contained curcuminoids 250 mg, which consisted of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, in a ratio of 1.0:0.6:0.3, respectively, confirmed by high-performance liquid chromatography/mass spectrometry.

Enrolled patients were randomly allocated to receive placebo or curcuminoids 4 capsules 4 times/day (4 g/day) in addition to standard therapy beginning 3 days before the scheduled surgery and patients continued to receive the assigned treatment until 5 days after surgery. To assign patients to curcuminoids or placebo, a block randomization sequence was obtained by a statistical consultant who was not involved in the study. Assigned therapy was fully blinded; surgeons and investigators performing postoperative assessment were not aware of the randomization assignment.

All patients undergoing CABG were treated with standard therapy according to their physicians. Three surgeons

performed CABG in the present study. The surgical techniques were determined at the discretion of the individual surgeons. On-pump CABG procedures were performed in 62 patients (51.2%), of whom 31 (25.6%) underwent on-pump CABG with the heart beating and 31 (25.6%) underwent on-pump CABG with conventional cardioplegic arrest. Myocardial protection was done with antegrade and retrograde cold blood cardioplegia. Off-pump CABG was performed in the remaining patients. The conduits used in patients in this study included the internal mammary arteries, radial arteries, and saphenous veins.

Twelve-lead electrocardiograms were recorded before surgery, 24, 48, and 72 hours after surgery, and 30-day follow-up visit. Serial creatine kinase-MB levels were assessed before surgery, at 8, 16, 24, 48, and 72 hours after intensive care unit arrival, and whenever an ischemic event was suspected. N-terminal pro–B-type natriuretic peptide (NT–pro-BNP) level was assessed before surgery and on the 5th postoperative day.

To examine the effects of curcuminoids on inflammatory response and oxidative stress after surgery, C-reactive protein (CRP) level was assessed before surgery and on postoperative days 3 and 5. In addition, plasma malondialdehyde (MDA) level, a marker for oxidative stress, was assessed before surgery and on postoperative day 5 using the high-performance liquid chromatographic method.

The primary end point of the study was to demonstrate that curcuminoids decrease the incidence of in-hospital MI compared to placebo. The secondary end point was to examine the effects of curcuminoids on CRP, MDA, and NT–pro-BNP levels after surgery.

The diagnosis of Q-wave MI was determined by the presence of new pathologic Q waves according to Minnesota Code criteria or new-onset left bundle branch block and creatine kinase-MB increase more than fivefold the upper normal limit of the investigators' local laboratory within 24 hours of CABG. In the absence of the aforementioned electrocardiographic findings, creatine kinase-MB increase >10-fold the upper normal limit within 24 hours of CABG was considered indicative of non–Q-wave MI.[7] If MI was suspected >24 hours after CABG, a creatine kinase-MB increase >2 times the upper normal limit with chest pain or an increase >3 times the upper normal limit was considered indicative of MI.[8]

All analyses were done on an intention-to-treat basis. Demographic and perioperative variables were compared between groups with *t* test for normally distributed values; otherwise the Mann–Whitney *U* test was used. Proportions were compared by chi-square test or Fisher's exact test when appropriate. Continuous variables are presented as mean ±SD or median ± interquartile range when appropriate. Categorical variables are displayed as percentages. Hazard ratios and 95% confidence intervals to assess the risk of the primary end point according to potential confounding variables were determined by logistic regression. Multivariate analyses were performed for variables with a p value <0.1 in univariate analysis using the logistic regression procedure. A p value <0.05 (2-tailed) was considered statistically significant.

Table 3
Multivariable logistic regression for myocardial infarction after coronary artery bypass grafting

Risk Factor	OR (95% CI)	*p* Value
Curcuminoid therapy	0.35 (0.13–0.95)	0.038
On-pump coronary artery bypass grafting	5.23 (1.92–14.28)	0.001

CI = confidence interval; OR = odds ratio.

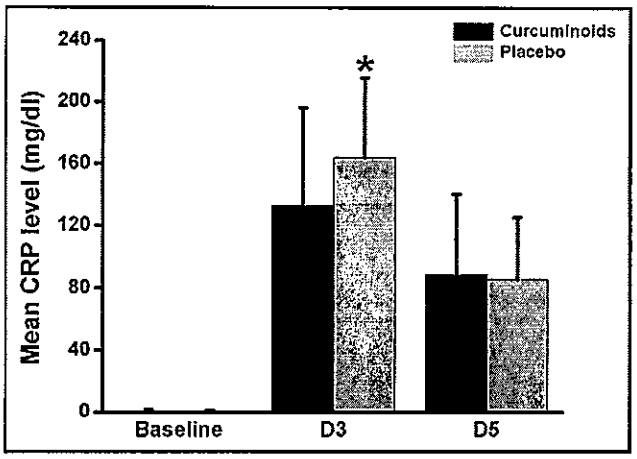

Figure 1. C-reactive protein levels before and after coronary artery bypass grafting in curcuminoid and placebo groups. C-reactive protein level on postoperative day 3 (D3) was significantly lower in the curcuminoid group compared to the placebo group. *p <0.05 versus placebo. D5 = postoperative day 5.

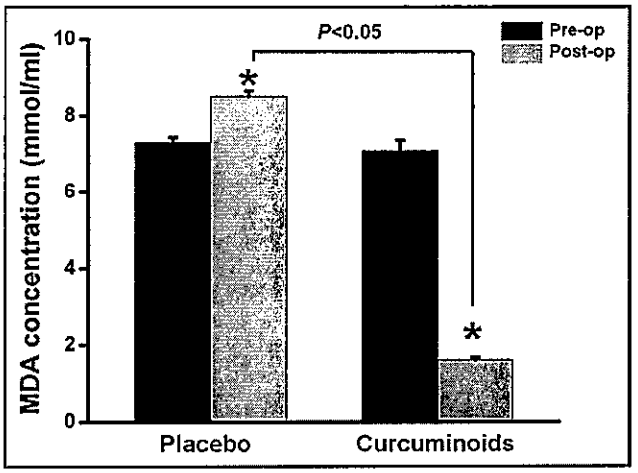

Figure 2. Levels of plasma malondialdehyde before (Pre-op) and after (Post-op) coronary artery bypass grafting in curcuminoid and placebo groups. Plasma malondialdehyde level increased after coronary artery bypass grafting in the placebo group but decreased significantly after coronary artery bypass grafting in the curcuminoid group. *p <0.05 versus preoperatively.

Results

Demographic and perioperative variables are presented in Tables 1 and 2, respectively. From September 2009 to December 2011, 121 consecutive patients who met the inclusion criteria were randomly divided to a curcuminoid group (n = 61) or a control group (n = 60). Baseline characteristics of patients in the 2 treatment groups were

Table 4
Adverse events and study drug discontinuation

Characteristics	Curcuminoid (n = 61)	Placebo (n = 60)	*p* Value
Adverse events			
Nausea	8 (13.1%)	5 (8.3%)	0.559
Diarrhea	2 (3.3%)	2 (3.3%)	1.000
Abdominal pain	3 (4.9%)	1 (1.7%)	0.619
Dizziness	2 (3.3%)	1 (1.7%)	1.000
Sore throat	1 (1.6%)	1 (1.7%)	1.000
Serious adverse events of special interest			
Serum creatinine increase*	4 (6.6%)	2 (3.3%)	0.691
Liver function			
Alanine aminotransferase or aspartate aminotransferase >3× upper limit of normal range	0 (0%)	2 (3.3%)	0.469
Alanine aminotransferase or aspartate aminotransferase >3× upper limit of normal range with concurrent bilirubin >2× upper limit of normal range	0 (0%)	1 (1.7%)	0.993
Inotrope requirement	43 (70.5%)	44 (73.3%)	0.884
Intra-aortic balloon pump usage	0 (0%)	4 (6.7%)	0.057
Severe postoperative hemorrhage required reoperation to stop bleeding	1 (1.6%)	1 (1.7%)	1.000
Stroke/transient ischemic attack	2 (3.3%)	1 (1.7%)	1.000
Death	1 (1.6%)	1 (1.7%)	1.000
Premature study drug discontinuation			
Overall	14 (22.9%)	11 (18.3%)	0.654
Owing to adverse drug events	6 (9.8%)	4 (6.7%)	0.743
By subject's request	7 (11.5%)	6 (10.0%)	1.000
For other reasons	1 (1.6%)	1 (1.7%)	1.000

* Increase in serum creatinine of ≥50%.

comparable including age, gender, co-morbidities, and previous percutaneous coronary revascularization (Table 1). Perioperative features were not different between the curcuminoid and placebo groups (Table 2).

Incidence of the primary outcome (in-hospital MI) was decreased from 30.0% in the placebo group to 13.1% in the curcuminoid group (unadjusted hazard ratio 0.35, 0.14 to 0.89, p = 0.028). Most MI events were non–Q-wave MI (Table 2). Apart from curcuminoid treatment, other predictors of in-hospital MI were identified. We found that on-pump CABG was significantly associated with a higher incidence of MI compared to off-pump surgery (35.5%, 22 of 62, vs 6.8%, 4 of 59, respectively, p <0.001). After multivariate analysis, we found that curcuminoid therapy remained the independent protective factor of in-hospital MI and that on-pump CABG was the independent predictive factor of in-hospital MI (Table 3). Of 121 patients, 57 patients underwent echocardiography 1 month after surgery. Incidence of postoperative left ventricular dysfunction (left ventricular ejection fraction <40%) was significantly higher in the placebo group than in the curcuminoid group (25.9%, 7 of 27, vs 3.3%, 1 of 30, respectively, p = 0.021).

Baseline preoperative CRP, MDA, and NT–pro-BNP levels were not different between the curcuminoid and placebo groups. However, mean increase in CRP level on postoperative day 3 compared to baseline level was significantly greater in the placebo group than in the curcuminoid group (difference +161.8 ± 54.1 vs +128.6 ± 60.5 mg/dl, respectively, p = 0.031; Figure 1). Plasma MDA level was increased after CABG in the placebo group but was decreased significantly after CABG in the curcuminoid group (difference +0.8 ± 1.4 vs −5.7 ± 1.5 mmol/ml, respectively, p <0.001; Figure 2). Furthermore, mean increase in postoperative NT–pro-BNP level compared to preoperative level was greater in the placebo group than in the curcuminoid group (difference +2,542.2 ± 2,631.2 vs +1,822.1 ± 2,102.9 pg/ml, respectively, p = 0.015).

Incidence of drug-related adverse events was not different between the curcuminoid and placebo groups (Table 4). The main drug-related adverse events were gastrointestinal symptoms. Incidences of serious adverse events and drug discontinuation did not differ between the 2 groups.

Discussion

Adequate myocardial protection during CABG is crucial in preventing myocardial injury after surgery.[7,9] Previous studies have shown that an increase of cardiac enzymes after CABG is associated with increased long-term mortality.[10] Nevertheless, some interventions reported to be cardioprotective in experimental models of ischemia/reperfusion injury have failed to translate their protective effects into clinical studies.[11] Until recently, only few clinical studies have shown promising results.[7,12–14] Mangano et al[14] recently examined the efficacy of the adenosine-regulating agent acadesine in patients undergoing CABG. They demonstrated that acadesine improved long-term survival in this group of patients. Furthermore, cariporide, the sodium-hydrogen exchange inhibitor, has been shown to decrease the incidence of MI associated with CABG, although the neurologic complications observed with the high dose preclude its clinical use.[7]

Preclinical data have shown that curcuminoids have cardiovascular protective effects in experimental models of various cardiac conditions.[15] In the present study, we demonstrated that curcuminoids decreased the incidence of in-

hospital MI after CABG significantly. In addition, curcuminoids attenuated postoperative NT–pro-BNP levels and decreased the incidence of postoperative left ventricular dysfunction. Accumulating evidence has suggested that curcuminoids have a diverse range of molecular targets and influence numerous biochemical and molecular cascades.[2] We propose that the beneficial effects of curcuminoids in the decrease of MI may be exerted by several mechanisms. First, it has been suggested that oxidative stress and systemic inflammatory response during cardiopulmonary bypass may account for ischemia/reperfusion injury occurring in patients receiving CABG. Curcuminoids have been shown to possess striking antioxidant and anti-inflammatory properties and to inhibit such mediators of inflammation as nuclear factor-κB, cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase.[16] Correspondingly, in the present study, we demonstrated that curcuminoids decreased postoperative CRP and MDA levels significantly. Therefore, the anti-inflammatory and antioxidative effects of curcuminoids may attenuate myocardial injury associated with cardiac surgery. Second, curcuminoids may protect against cardiac injury through a membrane-stabilizing effect.[17–20] Nirmala and Puvanakrishnan[4,21] demonstrated that curcuminoids significantly attenuated increased lysosomal hydrolase activity in serum and myocardial tissue in isoproterenol-induced MI in rats. Histopathologic findings also showed that the curcuminoid treatment decreased the degree of myocardial necrosis in isoproterenol-administered rats.[4] The membrane-stabilizing effect of curcuminoids may protect cells from autolytic and heterolytic damage and may attenuate the tissue damage owing to myocardial ischemia. Third, additional evidence from in vitro studied has shown that curcuminoids inhibit human platelet activation.[21,22] The antiplatelet property of curcuminoids may potentially decrease the occurrence of myocardial ischemia.

Because of the relatively small studied population, our results need to be confirmed in larger studies. Apart from the anti-inflammatory and antioxidant effects of curcuminoids shown in this study, other mechanisms of cardioprotective effects of curcuminoids are not clearly elucidated. Furthermore, the effect of curcuminoids on long-term outcome after CABG is unknown. Future studies are warranted to clarify this issue.

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