The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: A prospective randomized trial

Kriengchai Prasongsukarn, MD, MSc, James G. Abel, MD, MSc, W. R. Eric Jamieson, MD, Anson Cheung, MD, James A. Russell, MD, Keith R. Walley, MD, and Samuel V. Lichtenstein, MD, PhD

Objective: Atrial fibrillation remains one of the most common postoperative complications of coronary artery bypass grafting. Despite many clinical studies, there is still no consensus regarding the best prevention strategy for atrial arrhythmia. A randomized, double-blind, placebo-controlled trial was conducted to determine the effect of steroids on the occurrence of atrial fibrillation after elective coronary artery bypass grafting.

Methods: Eighty-eight consecutive patients were prospectively entered in this study. No patient had documented or suspected arrhythmias before surgery. Forty-three patients received 1 g of methylprednisolone before surgery and 4 mg of dexamethasone every 6 hours for 1 day after surgery, and 43 patients received only placebo. The primary end point was the overall occurrence of postoperative atrial fibrillation.

Results: Postoperative atrial fibrillation occurred in 9 (21%) of the 43 patients in the steroid group, as compared with 22 (51%) of the 43 patients in the placebo group ($P = .003$). Minor postoperative complications occurred in 15 steroid patients (35%) and in 6 patients (14%) receiving placebo ($P = .01$). Major complications occurred in 4 patients who received steroids (9%) and in 2 patients (5%) who received placebo ($P = .68$; for all complications, $P = .05$).

Conclusions: Prophylactic short-term steroid administration in patients undergoing coronary artery bypass grafting significantly reduced postoperative atrial fibrillation. In this study, there was no significant difference between the steroid group and the placebo group with regard to the length of hospital stay; however, the steroid group had more complications, which may contribute to prolonged hospitalization.

From St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada.

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Address for reprints: Samuel V. Lichtenstein, MD, PhD, St Paul's Hospital, 1081 Burrard St, Vancouver, BC, V6Z 1Y6 Canada (E-mail: SLichtenstein@providencehealth.bc.ca).

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Atrial fibrillation is a common complication of cardiac surgery during the first postoperative week, with an occurrence ranging from 20% to 50% of patients undergoing coronary artery bypass grafting (CABG).¹⁻⁸ The pathophysiologic mechanism of postoperative atrial fibrillation remains unknown; however, a multifactorial etiology is likely. These mechanisms include increased catecholamines; acute atrial distention or inflammation from the trauma of the operation; alteration in autonomic tone from the operation and the stress of the postoperative period; ischemic injury to the atria as a result of the operation or inadequate protection during cardiopulmonary bypass (CPB); electrolyte and volume shifts during CPB, resulting in changes in repolarization; inflammation resulting from pericarditis; and a variety of other electrophysiologic changes that may occur as a result of the CPB procedure, the cardioplegia, or the operation itself, all of which may result in a lower atrial fibrillation threshold.^{6,7,9,10}

A variety of pharmacologic agents have been used to prevent the occurrence of atrial fibrillation, including β -adrenergic blockers, amiodarone, and magne-

sium.¹¹⁻¹⁹ Because of the multifactorial etiology of postoperative atrial fibrillation and the well-known inflammatory response to CPB, steroids with the ability to inhibit inflammatory mediators—including interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)- α , leukotriene B₄, and tissue plasminogen activator—might have a beneficial effect in decreasing postoperative atrial fibrillation after CABG. The purpose of this study was to assess the use of short-term steroids as prophylaxis against atrial fibrillation after CABG.

Methods

From August 1, 2000, to February 28, 2001, 88 patients were screened and randomized for participation in this study. Inclusion criteria consisted of informed consent, age greater than 18 years, elective first-time CABG, β -adrenergic blockade, and normal sinus rhythm. Exclusion criteria included a history of heart block; a permanent pacemaker; any documented or suspected supraventricular or ventricular arrhythmias, including isolated atrial or ventricular premature depolarization noted on preoperative surface electrocardiography; requirement for additional procedures, such as valvular operation or left ventricular aneurysmectomy; refusal to participate in this study; use of a radial artery for grafting; steroid dependency; steroid allergy; and participation in another investigational protocol.

In a supplementary component of the study, we measured the cytokine concentrations and compared the measurements between groups. Concentrations of TNF- α , IL-6, IL-8, and IL-10 were measured with enzyme-linked immunosorbent assay at 4 and 24 hours after surgery in a subset of 22 patients in the steroid group and in 86 similarly treated control patients. Standard enzyme-linked immunosorbent assay measurements were made by using capture and detection antibodies obtained from Pharmingen (San Diego, Calif) that for TNF- α were 18631D 2 μ g/mL and 18642D 1 μ g/mL, for IL-6 were 18871D 1 μ g/mL and 18882D 1 μ g/mL, for IL-8 were 20781D 1 μ g/mL and 20792D 1 μ g/mL, and for IL-10 were 20701D 1 μ g/mL and 18562D 1 μ g/mL.

Study Protocol

The study design was approved by the Clinical Research Ethics Board of the University of British Columbia/Providence Health Care and was a double-blind protocol in which the surgical staff, principal investigators, and patients were blinded to the assigned therapy. Clinical data were collected and recorded in the database by independent blinded investigators.

Patients were randomly assigned in a double-blind fashion either to a placebo group receiving maintenance fluids (5% dextrose water with potassium chloride 20 mEq/L) or to a steroid group receiving 1 g of intravenous methylprednisolone sodium succinate (Solu-Medrol; Upjohn, Kalamazoo, Mich) before CPB and 4 mg of intravenous dexamethasone (Decadron; Merck Sharp & Dohme, West Point, Pa) every 6 hours for a total of 4 doses in the first 24 hours after surgery. All vials of the steroid and placebo medications were prepared and randomized by the hospital phar-

macy. The steroid and placebo solutions were visually indistinguishable.

Operative Technique

Standardized anesthesia and surgical protocols were applied in all cases. All operations were performed by using normothermic (37°C) CPB with antegrade warm-blood cardioplegia. CPB was performed with aortic and right atrial cannulation, membrane oxygenation, and nonpulsatile flow. Standard surgical techniques were used to create the distal coronary anastomoses first; proximal anastomoses followed for saphenous vein grafts, and internal thoracic artery grafts were conducted after distal venous anastomoses.

After weaning from CPB, inotropic support was initiated when needed to maintain cardiac contractility, if the cardiac index was less than 2 L $\cdot$ min⁻², or if the mean arterial pressure was less than 70 mm Hg. Electrical pacing was instituted (atrial or atrioventricular) when needed to maintain a heart rate greater than 70 beats/min. Patients were continuously monitored in the cardiac surgery intensive care unit. Patients were weaned off mechanical ventilation on the basis of hemodynamic stability, blood gas analysis, and level of alertness. Discharge from the cardiac surgery intensive care unit was generally accomplished after extubation and the discontinuation of all vasoactive medications.

Patients receiving β blockade, digitalis, or calcium channel blockade had these medications continued until the day of operation. Standard postoperative medications were incorporated. Patients received the usual postoperative cardiac care, including β blockade to prevent atrial arrhythmias as a standard protocol.

Hemodynamic Measurement and Monitoring

Patients were continuously monitored in the cardiac surgery intensive care unit with arterial, central venous, and pulmonary artery pressure monitoring and thermodilution cardiac output determination. Cardiac rhythm was continuously monitored in the intensive care unit with bedside monitors and on the ward, after the intensive care unit until discharge, with telemetry.

Twelve-lead electrocardiograms were obtained immediately after surgery and on the first morning after the operation. Supraventricular and ventricular arrhythmias and their respective treatment interventions were documented and supported by the inclusion of rhythm strips in the patients' charts. The investigator reviewed all rhythm strips daily until the patients were discharged from the hospital. For the purpose of defining end points in this study, postoperative atrial fibrillation was defined as an irregularly irregular supraventricular rhythm present in the absence of P waves that required treatment and that was typically sustained for more than 15 minutes.

Episodes of atrial fibrillation were considered when they recurred or continued into the following 24-hour period as an additional episode. Arrhythmia data were collected and recorded for the first 7 postoperative days.

According to these definitions, cardiac arrhythmias were treated under the direction of the attending surgeon. Standardized protocols for the treatment of supraventricular and ventricular arrhythmias were adhered to during the study. Blood gas abnormalities were corrected. Potassium, magnesium, and calcium were administered as needed to maintain serum concentrations greater than 4 mmol/L, 1.5 mEq/L, and 8.5 mg/dL, respectively. Thera-

peutic approaches for treatment of postoperative atrial fibrillation included standard pharmacologic management and electric cardioversion if indicated.

Patients were routinely anticoagulated with heparin, warfarin, or both when atrial fibrillation persisted for longer than 36 hours. Patients were followed up with a routine protocol on the ward until discharge from the hospital. The length of hospital stay was calculated from the day of operation until the day of discharge.

Statistics

The null hypothesis was that there was no difference in the occurrence of postoperative atrial fibrillation between therapy with short-term steroids and placebo. With the occurrence of postoperative atrial fibrillation after CABG in our hospital of 43.5%, a sample size of 168 patients was estimated to be sufficient to detect a 50% reduction in the steroid treatment group with a power of 80% and a 2-sided type I error of 0.05. The primary end point was the occurrence of postoperative atrial fibrillation. Secondary end points were the length of hospital stay and the adverse effects (complications) of steroids.

Comparison of continuous variables across the 2 treatment groups was accomplished with a 2-sample *t* test or a Wilcoxon rank sum test where appropriate. Comparison of categorical variables across the 2 groups was analyzed with χ^2 or Fisher exact tests (where applicable). A logistic regression analysis was performed to compare the 2 groups with possible confounders adjusted. The cytokine data analysis was conducted with log transformation by 2-way analysis of variance: 1 way with repeated measures (2 cytokine time points) and the other way between groups (steroid or not).

Statistical analysis was performed with SAS software (SAS Institute, Cary, NC). The frequencies were presented with the 95% confidence limits (CL).

Interim Analysis

A planned interim analysis was performed after 50% enrollment to assess prospectively determined criteria for termination. This analysis revealed that the difference in the primary outcome variable between treatment groups had crossed the statistical boundary for breaking the code interim analysis. The analysis revealed a significant reduction of the occurrence of postoperative atrial fibrillation after CABG in the steroid group and revealed no identified detrimental effect of the steroid. Therefore, study enrollment was terminated on February 28, 2001; 88 patients had been randomly assigned to the groups, and the code was broken. Medical history, demographic data, and clinical course data were collected for each patient. Criteria for termination of the study were based on the O'Brien-Fleming spending function, the *P* value for the interim analysis was .005, and the *P* value for the final analysis for all patients was .048.

Results

This randomized, prospective clinical trial was performed in 88 patients: 2 patients were excluded from the study because they had off-pump CABG surgery, 43 patients received a steroid, and 43 patients received placebo. Selected

TABLE 1. Clinical characteristics of the steroid and placebo groups

Variable	Steroid group	Placebo group	<i>P</i> value
No.	43	43	
Sex (F/M)	10/33	10/33	1.0
Age (y)	67.2 (64.5-70)	61.7 (58.6-64.8)	.007
History of MI	28	28	1.0
Asthma	6	1	.11
COPD	10	6	.27
CHF	9	11	.61
HTN	27	23	.38
Smoking	17	17	1.0
CRF	2	2	1.0
LVEF	37.8 (20-71)	49.2 (20-74)	.03
Crossclamp time	66 (57-75)	71 (62-80)	.39
Atrial pacing	8	13	.21
Atrioventricular pacing	7	1	.06

MI, Myocardial infarction; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; HTN, hypertension; CRF, chronic renal failure; LVEF, left ventricular ejection fraction. Age, LVEF, and crossclamp time are given as mean (range).

TABLE 2. Incidence of postoperative atrial fibrillation (AF) in the steroid and placebo groups

Group	Patients, n (%)		Total
	No AF	AF	
Steroid*	34 (79.1%)	9 (20.9%)	43
Placebo	21 (48.8%)	22 (51.2%)	43
Total	55	31	86

**P* = .003.

patient demographics are presented in Table 1. Statistically significant differences were found in age and left ventricular ejection fraction between groups. Other variables were not different between treatment groups. There were no deaths in the study period.

Postoperative Atrial Fibrillation

The percentages of the occurrence of postoperative atrial fibrillation in patients in both groups are shown in Table 2. The occurrence of postoperative atrial fibrillation was 20.93% (95% CL, 8.77%-33.09%; 9 of 43 patients) in the short-term steroid group, as compared with 51.16% (95% CL, 36.22%-66.1%; 22 of 43 patients) in the placebo group (*P* = .003).

Length of Hospital Stay

Patients with normal sinus rhythm had a shorter length of hospital stay than those with atrial fibrillation (median, 6 vs 8 days, respectively; *P* = .002). However, there was no

TABLE 3. Complications in the steroid and placebo groups

Variable	Steroid group	Placebo group
GI disturbance	4	1
High blood sugar	4	—
Mental confusion	2	2
Increased postoperative creatinine	1	1
UTI	2	—
Sternal wound infection	1	1
Leg wound infection	1	1
Intravenous line infection	1	—
Gastritis	—	1
Sternal dehiscence*	2	2
Acute pancreatitis*	1	—
Perforated GU*	1	—

GI, Gastrointestinal; UTI, urinary tract infection; GU, gastric ulcer. *Major complications (some patients had more than 1 complication).

TABLE 4. Major and minor complications in the steroid and placebo groups

Group	Complications, n (%)			Total
	None	Major	Minor	
Steroid	24 (55.8%)	4 (9.3%)	15 (34.88%)	43
Placebo	35 (81.4%)	2 (4.65%)	6 (13.95%)	43
Total	59	6	21	86

Minor complications, $P = .01$; major complications, $P = .68$; overall complications, $P = .05$.

statistically significant difference in the length of hospital stay between the 2 groups (median of 6 days in the steroid group as compared with 7 days in the placebo group; $P = .34$).

Complications

Major complications included severe sternal infection requiring rewiring, acute pancreatitis, and perforated gastric ulcer. Minor complications are listed in Table 3.

The data analysis showed that the steroid group had more minor complications (34.88%; 95% CL, 23.19%-53.73%) than the placebo group (13.95%; 95% CL, 3.82%-25.42%) ($P = .01$), but there was no statistically significant difference in major complications (9.3%; 95% CL, 0.62%-17.98% vs 4.65%; 95% CL, 0%-10.95%, respectively) ($P = .68$) or overall postoperative complications (overall $P = .053$; Tables 3 and 4).

There was a significant difference in the white blood cell count at 12 and 24 hours after surgery. It was apparent that the steroid group had higher white blood cell counts at 12 and 24 hours (median, 6.5 and 8.45 G/L, respectively) than

the placebo group (median, 2.7 and 2.5 G/L, respectively; $P < .0001$).

Cytokine Measurement

The concentrations of TNF- α , IL-8, and IL-10 at 4 and 24 hours after surgery were not statistically significantly different between the steroid and control groups. However, the steroid group had significantly reduced IL-6 concentrations at both 4 and 24 hours after surgery compared with controls. At 4 hours, IL-6 in the steroid group was 593.2 ± 95.5 pg/mL versus 1206.8 ± 255.6 pg/mL in the control group ($P = .04$), and at 24 hours IL-6 in the steroid group was 316.6 ± 64.2 pg/mL versus 570.7 ± 68.2 pg/mL in the control group ($P = .01$). The difference of IL-6 with time had a P value of less than .001, and the difference in IL-6 between the steroid group and nonsteroid group had a P value of less than .009.

Discussion

Prophylactic short-term steroid administration in patients undergoing CABG reduced the occurrence of postoperative atrial fibrillation by approximately 50%. Because of statistically significant differences in 2 baseline characteristics in the 2 groups—advancing age and low ejection fraction in the steroid group, which are considered the risk factors of postoperative atrial fibrillation—the efficacy of steroids might be stronger than was evident. Creswell and associates⁵ found that advancing age and low ejection fraction were risk factors of postoperative atrial fibrillation by univariate logistic regression analysis.

Our findings supported the recent report by Yared and colleagues²⁰ of a lower incidence of new-onset atrial fibrillation with the administration of dexamethasone 0.6 mg/kg after the induction of anesthesia. However, the study by Halvorsen and colleagues²¹ showed that dexamethasone (8 mg in divided doses) was beneficial in reducing emetic symptoms and improving appetite after cardiac surgery but had no effect on the occurrence of postoperative atrial fibrillation. This may be explained by the different doses of corticosteroids administered in each study.

In this study, patients without postoperative atrial fibrillation had a shorter length of hospital stay. Overall, there was no significant difference between the steroid group and the placebo group with regard to the length of hospital stay. Data showed that the steroid group had more complications, which may contribute to prolonged hospitalization.

Although there was statistically significant difference in minor complications between the steroid group and the placebo group, there was no statistically significant difference in major and overall complications. However, there was a trend toward more complications in the steroid group. In this study, 4 patients had high glucose intolerance that necessitated consultation with an endocrinologist to control

blood glucose. Mayumi and colleagues²² showed that glucose intolerance was worsened by steroids during CPB. This might be a disadvantage of steroid use.

Infection is another complication that can be a concern with steroid administration. In this study, we found infection in both groups, with no statistically significant difference. The white blood cell count was increased significantly in the steroid group at 12 and 24 hours after surgery.

However, the white blood cell count 5 days after surgery had returned to the preoperative level. This can be explained by the demargination process of white blood cells, which could be effected by the steroid.

Many studies have documented the adverse effects of CPB, and some studies claim an advantage of steroid use in cardiac surgery.^{23,24} Jansen and associates²⁵ showed that steroids could inhibit TNF and leukotriene release, and these are the primary mediators involved in reperfusion phenomena and sepsis. In that study, steroids improved the postoperative course after CPB.

Teoh and associates²⁶ found that steroids decreased cytokine release and the vasodilation effect. Engelman and colleagues²⁷ found the same result and recommended prophylactic steroid use in open-heart surgery. The dose recommended by Engelman and colleagues was used in this study. The steroid doses maintained therapeutic steroid effects for 4 days, which covers the peak incidence of postoperative atrial fibrillation. Engelman and colleagues did not find any adverse effects of steroid use, possibly because of their small sample size (10 steroid and 9 placebo patients).

Recent investigations have indicated that cytokines play a key role in the inflammatory cascade associated with CPB. The levels of TNF- α , IL-6, and IL-8 were correlated with the duration of cardiac ischemia, and the myocardium is a major source of these cytokines during CPB.²⁸ Proinflammatory cytokines such as IL-6 and IL-8 were associated with postoperative myocardial dysfunction and the outcome of cardiac surgery.²⁹ In our study, we found that short-term steroid administration reduced the IL-6 concentrations at both 4 and 24 hours after surgery. This might improve the outcome of cardiac surgery.

The median length of hospital stay for patients with atrial fibrillation was 8 days, compared with 6 days in patients with normal sinus rhythm. However, the median length of hospital stay of the steroid group was 6 days, and in the placebo group it was 7 days. This could be explained by the increased length of hospital stay in the steroid group. Two patients with major complications in the steroid group had 30- and 32-day hospital stays, and this made a significant difference between patients with and without complications.

In our study, only advanced age was consistently associated with an increased risk of postoperative atrial fibrillation by multivariate logistic regression analysis. Creswell

and associates⁵ found that chronic obstructive lung disease and crossclamp time were the risk factors for the development of postoperative atrial fibrillation. This might be related to the sample sizes (86 vs 4507 patients). Also, we found that there was no statistically significant difference in atrial pacing and postoperative atrial fibrillation.

Limitations of the Study

Our study was a double-blind randomized controlled trial, and the design and reporting of the study were compatible with the Consolidated Standards of Reporting Trials statement.³⁰ However, there were 2 issues of concern in the study. As the results showed, steroids conferred a beneficial effect on the occurrence of postoperative atrial fibrillation after CABG. There was a slight increase in the postoperative complications; even the *P* values did not show any statistically significant difference. Some might say that we should have continued the study and gathered more data to evaluate safety and efficacy. However, at the commencement of our study, we decided to perform the interim analysis, and our primary end point was the occurrence of postoperative atrial fibrillation.

After 50% enrollment, the code was broken, and the data showed that the primary outcome was satisfied, so we agreed to stop the study. It would be appropriate to design another study to see whether steroids in different dosages can improve both primary and secondary outcomes. Another issue in our study was the cytokine levels. With limited funding in this study, we could include only 22 patients in the steroid group to compare with the previous data in a control group. We found in our study that steroids can inhibit IL-6, which is correlated with the postoperative outcome in cardiac surgery. However, we did not correlate IL-6 with the incidence of postoperative atrial fibrillation after CABG, probably because of the small sample size. With a larger sample size, we might find some correlation between postoperative atrial fibrillation and IL-6. That might be the cause of postoperative atrial fibrillation after CABG.

In conclusion, with the high degree of efficacy of steroids in decreasing postoperative atrial fibrillation but with slightly increased complications, we could try to adjust the steroid dose (for example, give half the dose of methylprednisolone [500 mg, as given in heart transplant recipients]) or use prophylactic steroids for patients who are at high risk of developing postoperative atrial fibrillation, such as older patients or those with long-crossclamp-time operations, low ejection fraction, chronic obstructive pulmonary disease, preoperative use of digoxin, or valvular disease. We could also use prophylactic steroids with patients who do not have diabetes mellitus. Subsequently, we can redesign other studies for prophylactic steroid administration for postoperative atrial fibrillation, such as high- versus low-dose steroid use,

steroid in patients at high risk for atrial fibrillation, steroid combined with β blockade, steroid combined with amiodarone, and steroid with biatrial pacing. It is hoped that, with further study, the best prevention for postoperative atrial fibrillation can be identified.

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