Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Effect of a Single Bolus Injection of Low-Dose Hydrocortisone for Prevention of Atrial Fibrillation Recurrence After Radiofrequency Catheter Ablation

Hoyoun Won, MD; Jong-Youn Kim, MD; Jaemin Shim, MD; Jae-Sun Uhm, MD; Hui-Nam Pak, MD, PhD; Moon-Hyoung Lee, MD, PhD; Boyoung Joung, MD, PhD

Background: The transient use of corticosteroid shortly after atrial fibrillation (AF) ablation might prevent immediate and mid-term AF recurrence; however, the effective dosage for preventing AF recurrence has not been determined. In this study, we evaluated whether low-dose hydrocortisone is effective for the prevention of AF recurrence after radiofrequency catheter ablation (RFCA).

Methods and Results: We enrolled 89 AF patients (70 males, 55.8±10.9 years) who underwent RF ablation and were treated with single bolus injection of 100 mg hydrocorticosteroid (corticosteroid group). For the control group, we enrolled 120 sex- and age-matched AF patients (94 males, 55.4±10.5 years). Pericarditis occurred in 3 (2.5%) and 1 (1.1%) patients in the control and corticosteroid groups, respectively. The number of patients with immediate AF recurrence (≤2 days) was 17 (14.5%) and 11 (12.4%) in the control and steroid groups, respectively (P=0.687). Treatment with low-dose steroid did not decrease early (3–30 days) AF recurrence (13 [11.1%] vs. 11 [12.5%], P=0.829) or late (≥31 days) AF recurrence after ablation (26 [22.2%] vs. 13 [14.6%], P=0.209). There was no difference in cumulative survival free of late AF recurrence between the corticosteroid and control groups (P=0.57 by log-rank test). White blood cell count, C-reactive protein concentration and maximum body temperature also were unchanged by low-dose steroid.

Conclusions: Single bolus injection of low-dose hydrocortisone after AF ablation is not effective for preventing AF recurrence during the mid-term follow-up period. (*Circ J* 2013; **77:** 53–59)

Key Words: Atrial fibrillation; Catheter ablation; Corticosteroid; Recurrence

Radiofrequency catheter ablation (RFCA) is an effective treatment for drug-refractory atrial fibrillation (AF), with promising success rates. However, there is still a chance of AF recurrence, especially within the first few weeks after ablation.[1] The relationship between inflammation and development of AF has been studied.[2,3] An increase in the baseline C-reactive protein (CRP) concentration suggests preexisting myocardial inflammation, which may be a marker of increased proinflammatory response after surgery. Corticosteroids are potent inhibitors of the proinflammatory cascade and have been shown to limit the increase in interleukin (IL)-6, IL-8, tumor necrosis factor α, CRP, and oxygen free radicals after cardiac surgery.[4–6]

Inflammation and oxidative stress are the leading pathogenic mechanisms in special forms of AF (eg, postoperative AF),[7] but they are also involved in AF in the general population and in senile AF.[8,9] Because atrial myocardial destruction occurs during RFCA for AF, an acute inflammatory response is likely to develop.[10,11] However, evidence for the use of corticosteroids as upstream therapy for secondary prevention of AF is sparse. Recently, transient use of corticosteroids shortly after AF ablation was reported to be effective and safe for preventing AF recurrence during the mid-term follow-up period after pulmonary vein isolation (PVI).[12] There is increased risk of hyperglycemia, postoperative pneumonia, urinary tract infections, and gastrointestinal bleeding after steroid therapy. In addition, high-dose steroids may cause ventricular proarrhythmia and even promote AF.[13,14] These potential adverse effects deter the routine use of corticosteroids for prevention of AF after cardiac surgery, and corticosteroid therapy has been assigned as a Class IIb recommendation in the European Society of Cardiology guidelines.[15,16] However, the adequate dosage of steroid and the method of administrate have not been determined. This study evaluated the effect of a single bolus intravenous injection of a small dosage of hydrocorticosteroid on the recurrence of AF after RFCA.

Received June 4, 2012; revised manuscript received July 16, 2012; accepted August 20, 2012; released online September 22, 2012 Time for primary review: 13 days

Cardiology Division, Department of Internal Medicine, Yonsei University Medical College, Seoul, Republic of Korea
Mailing address: Boyoung Joung, MD, PhD, Associate Professor of Medicine, Yonsei University Health System, 250 Seungsanno, Seodaemun-gu, Seoul 120-752, Republic of Korea. E-mail: cby6908@yuhs.ac

ISSN-1346-9843 doi:10.1253/circj.CJ-12-0728

Methods

Patients

This study included 89 patients with drug-resistant AF who underwent RF ablation and were treated with corticosteroid at Yonsei University Hospital (Seoul, Korea) from July 2007 to December 2010. All patients were newly enrolled in this study, and none had a history of ablation. For the control group, we enrolled 120 sex- and age-matched AF patients who had undergone RF ablation of AF during the same period. Both groups included patients with only first-time ablation. All patients had symptomatic, paroxysmal or persistent AF. The selection of patients to be given steroid depended on the operators. A physician (B.J.) had the strategy of giving corticosteroid after catheter ablation, whereas the other physicians (M.-H.L. and H.-N.P.) did not give steroid. Patients were randomly assigned to operators without this information. However, the ablation protocol was the same for all the operators.

Paroxysmal AF was defined as AF episodes that spontaneously terminated and lasted for >30 s and <7 days during treatment with antiarrhythmic drugs (AADs). Persistent AF was defined as AF episodes that either lasted longer than 7 days or that required termination by cardioversion, either with AADs or by direct current cardioversion. All AADs were discontinued 5 half-lives before the ablation procedure, and other drugs were administered throughout the duration of the study period.

The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, Seoul, Korea and complied with the Declaration of Helsinki.

Study Protocol

This study was a double cohort study. In the corticosteroid group, 100 mg hydrocortisone sodium succinate (Solu-Cotef, Pfizer Manufacturing, Puurs, Belgium) in 5 ml of a 0.9% sodium chloride solution was administered intravenously within 30 min after the procedure. Patients in the control group were not given any corticosteroid.

Within each group, the patients were divided into 3 subgroups according to the results of AF recurrence during the initial 1 month after ablation:[11,12] immediate AF recurrence group, early AF recurrence group, and non-AF recurrence group. Immediate and early AF recurrences were defined as AF episodes that occurred within 2 days and between 3 and 30 days after RFCA, respectively. Non-AF recurrence was defined as no AF after RFCA. The primary endpoint of the study was the proportion of patients free of recurrent AF, and the secondary endpoint was recurrent AF and any serious complications caused by catheter ablation or treatment with corticosteroid.

Catheter Ablation

The 3-dimensional geometry of the left atrium (LA) was reconstructed with a CARTO or NavX electroanatomic mapping system. Before ablation, triggers were evaluated after direct current cardioversion of AF. Circumferential PVI was performed in all patients using a 3.5-mm irrigated-tip catheter (ThermoCool, Biosense Webster, CA, US) with the maximum temperature set at 50° and a power output of 25–35 W. We used a circular mapping catheter (Lasso, Biosense Webster) to confirm PVI. The endpoint of the PVI was creation of a bidirectional conduction block from the LA to the PVs and vice versa. A cavo-tricuspid isthmus block line was created with confirmation of the bidirectional block. After the PVI, if AF was sustained or induced with coronary sinus burst pacing at a cycle length as short as 180 ms during the administration of intravenous isoproterenol (1.0–10.0 μg/min) and lasted more than 3 min, additional ablation, consisting of linear ablation, complex fractionated atrial electrogram (CFAE) ablation and/or superior vena cava (SVC) isolation, was performed.[17] If the AF did not terminate or was inducible after these procedures, sinus rhythm was restored by transthoracic cardioversion.[17]

Follow-up

Patients remained hospitalized under continuous rhythm monitoring (IntelliVue Telemetry System, Philips Healthcare, The Netherlands) for at least 48 h after the procedure and were followed after the RFCA. After discharge, all patients underwent follow-up at 1 week and 1 month post-procedure and then every 3 months thereafter. At each hospital visit, the patients underwent 12-lead ECG and intensive questioning regarding any arrhythmia-related symptoms (palpitation, chest discomfort and dizziness) since the previous follow-up visit. Holter monitoring for 24 h was performed at 1 and 3, 6, and 12 months after RFCA. Portable event ECG monitoring (EV-101, Parama-Tech, Fukuoka, Japan) was performed as arrhythmic assessment in patients with intermittent symptoms. We defined immediate recurrence as any episode of AF or atrial tachycardia (AT) of at least 30 s that occurred within 2 days after AF ablation, early recurrence between 3 and 30 days and late recurrence after 31 days, respectively.[11,12] Three patients in the control group who developed pericarditis after RFCA were excluded from the analysis of recurrence because they were treated with higher doses of corticosteroids.

If the ECG showed any AF episodes during follow-up, patients received a diagnosis of clinical recurrence of AF, irrespective of the presence of symptoms.[11] Patients with AF recurrence were treated temporarily with Class I, II, III, and/or IV AADs, and the AADs were discontinued if stable sinus rhythm could be maintained. Discontinuation of the AADs was then attempted in those patients in whom the recurrent AF disappeared after temporary treatment; if sinus rhythm could be maintained, the drugs were stopped permanently.

Other Definitions

The patient's body temperature (BT) was measured on the morning of the ablation and every 8 h for 72 h after the ablation using an eardrum thermometer (Infrared thermometer IRT4020, Braun GmbH, Kronberg, Germany) placed into the ear canal. The CRP concentration and complete blood cell count were measured 1 day after the catheter ablation.

Statistical Analysis

SPSS version 17.0 (SPSS Inc, Chicago, ILL, USA) was used for statistical analysis. Continuous variables are expressed as the mean ± standard deviation, and categorical variables were described using numbers or percentages. Comparisons of the differences between 2 groups were performed using the chi-square analysis and the unpaired Student's t-test. The time to AF recurrence 31 days after catheter ablation was estimated by the Kaplan-Meier method, with comparisons made using the log-rank test. A P value <0.05 was considered statistically significant.

Results

Baseline Characteristics

We enrolled 89 consecutive AF patients (70 males, 55±11 years) who underwent RF ablation and were treated with corticosteroid (corticosteroid group). For the control group, we enrolled 120 sex- and age-matched AF patients (94 males,

Table 1. Baseline Characteristics of the Study Group

	Control (n=120)	Corticosteroid (n=89)	P value
Age, years	55±11	55±11	0.78
Male (n, %)	94 (78)	70 (78)	0.96
Paroxysmal AF (n, %)	57 (48)	50 (56)	0.26
Comorbidities (n, %)			
Congestive heart failure	4 (3)	2 (2)	0.67
Hypertension	52 (44)	38 (45)	0.89
Age >75 years	2 (2)	2 (2)	0.73
Diabetes	16 (14)	4 (5)	0.04
Stroke	6 (5)	8 (9)	0.22
Coronary artery disease	10 (8)	4 (5)	0.46
Valvular heart disease	6 (5)	3 (3)	0.57
Echocardiographic parameters			
LA diameter, mm	41±6	43±5	0.07
LV end-diastolic dimension, mm	50±4	50±4	0.23
LV ejection fraction, %	63±8	63±7	0.52
Antiarrhythmic drugs			
Class Ic (n, %)	70 (58)	53 (60)	0.86
Class III (n, %)	45 (38)	27 (30)	0.28
Medications			
ACEIs or ARBs (n, %)	30 (25)	24 (29)	0.59
β-blockers (n, %)	21 (18)	20 (24)	0.28
Statins (n, %)	18 (15)	12 (14)	0.87

Values are expressed as mean±SD.
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; LA, left atrial; LV, left ventricular.

Table 2. Catheter Ablation

	Control (n=120)	Corticosteroid (n=89)	P value
Ablation procedure (n, %)			
Circumferential PV isolation	120 (100)	89 (100)	0.99
CTI ablation	112 (93)	86 (97)	0.36
Linear ablation			
Roof line	7 (6)	6 (7)	0.78
Posterior box	50 (42)	28 (32)	0.15
Mitral isthmus line	4 (3)	3 (3)	0.99
CFAE	1 (1)	0 (0.0)	0.39
SVC isolation	7 (6)	4 (5)	0.76
Catheter ablation			
Total duration of procedure, min	201±52	188±45	0.06
Total fluoroscopy time, min	48±16	47±21	0.50
Duration of RF ablation, min	89±32	82±28	0.01
Recurrence*			
Immediate (≤2 days)	17/117 (15)	11/89 (12)	0.69
Early (3–30 days)	13/117 (11)	11/89 (12)	0.83
Late (≥31 days)	26/117 (22)	13/89 (15)	0.21

Values are expressed as mean±SD.
*Three patients in the control group who developed pericarditis after RFCA were excluded from the analysis of recurrence because they were treated with corticosteroid.
CFAE, complex fractionated atrial electrogram; CTI, cavo-tricuspid isthmus ablation; Posterior box, roof line and additional posterior inferior line connecting the lower margins of the right and left PV lines; PV, pulmonary vein; RF, radiofrequency; Roof line, left atrial roof connecting the tops of the 2 encircling lesions of PV.

Table 3. Inflammation Markers, Body Temperature and Pericarditis

	Control (n=120)	Corticosteroid (n=89)	P value
WBC (/μL)	9,078±2,523	8,796±2,279	0.50
CRP (mg/L)	20.6±11.9	22.2±26.8	0.91
Maximum body temperature (°C)	37.1±0.4	37.0±0.5	0.27
Pericarditis (%)	3 (3%)	1 (1%)	0.47

CRP, C-reactive protein; WBC, white blood cells.

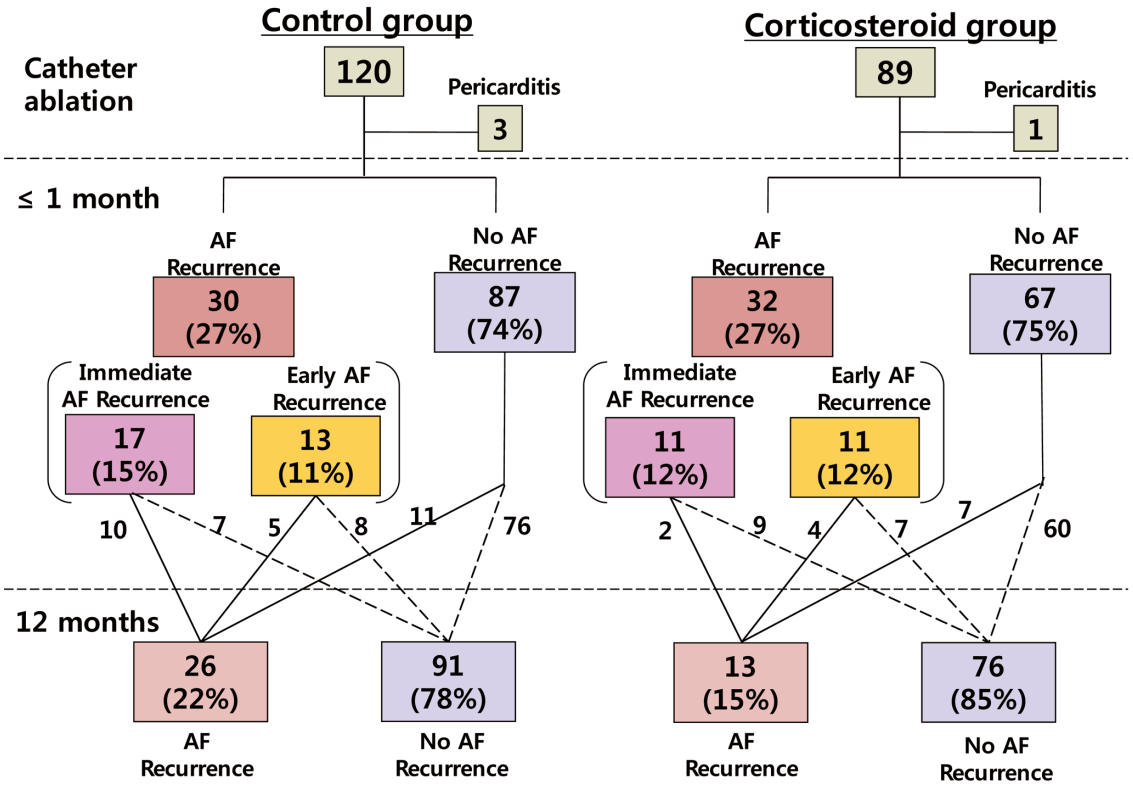

Figure 1. Flow diagram and outcome of radiofrequency catheter ablation for atrial fibrillation (AF).

55±11 years). Their baseline clinical characteristics are shown in Table 1. Comorbidities, medications, echocardiographic parameters, AADs and other medications were not significantly different between the 2 groups.

Ablation Procedure and Recurrence Rate of AF

Catheter ablation parameters and the recurrence rate of AF are presented in Table 2. Circumferential PVI was successfully performed in all patients, and bidirectional conduction block was created at all 4 PVs. A cavo-tricuspid isthmus block line with confirmation of bidirectional block was successfully created in 112 (93%) and 86 (97%) patients in the control and corticosteroid groups, respectively. There were no differences in linear ablation, CFAE or SVC isolation between the 2 groups. The duration of RF ablation was longer in the control (89±32 min) than in the corticosteroid group (82±28 min, P=0.01). The total duration of the procedure and fluoroscopy time was not different between the 2 groups.

The number of patients with immediate AF recurrence (≤2 days) was 17 (15%) and 11 (12%) in the control and steroid groups, respectively (P=0.69). Single bolus injection of hydrocortisone did not decrease early (3–30 days) AF recurrence (13 [11%] vs. 11 [12%], P=0.83) or late (≥31 days) AF recurrence after ablation (26 [22%] vs. 13 [15%], P=0.21). The immediate, early and late recurrent rates according to the type of AF were not significantly different.

Inflammatory Responses, Pericarditis, and Atrial Arrhythmias During the Initial 3 Days After Ablation

There was no difference between the 2 groups in the white blood cell (WBC) count (9,078±2,523 vs. 8,796±2,279/μL, P=0.50) or CRP concentration (20.6±11.9 vs. 22.2±26.8 mg/L, P=0.91) during the initial 3 days after ablation (Table 3). No significant differences were found in maximum BT (37.1±0.4 vs. 37.0±0.5°C, P=0.27) in the control and corticosteroid groups. Pericarditis occurred in 3 (3%) and 1 (1%) patients in the control and corticosteroid groups, respectively. Because the 3 patients with pericarditis in the control group were treated with

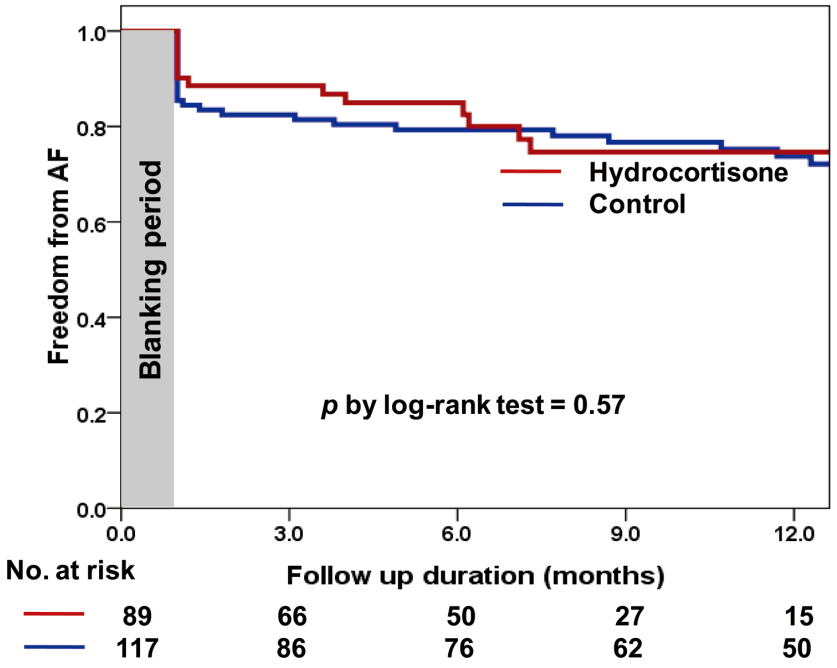

Figure 2. Kaplan-Meier survival curves for atrial fibrillation (AF) recurrence. There was no difference in cumulative survival free of late AF recurrence between the corticosteroid and control groups (P=0.570 by log-rank test).

steroids, they were excluded from the analysis of recurrence. WBC, CRP and maximum BT did not differ between paroxysmal and persistent AF patients. There was also no difference between the corticosteroid and control groups in AF recurrence in patient with higher CRP concentration (>10 mg/L) (unpublished data).

Post-Ablation Course and Resolution of AF Recurrences

During the ablation procedure and mean follow-up of 12 months, no major complications occurred in any patient. The rates of infection and hematoma were not different between the 2 groups. In the control group, AF recurrence disappeared in 7 (41%) of 17 patients with immediate AF recurrence and in 8 (62%) of 13 with early AF recurrence between 31 days and 12 months after RFCA (Figure 1). However, in the corticosteroid group, recurrent AF attacks disappeared in 9 (82%) of 11 patients with immediate AF recurrence and in 7 (64%) of 11 with early AF recurrence during the same period. Interestingly, the prevalence of an AF-free rate at 12 months post-ablation in the subgroup analysis of the patients with immediate AF recurrence was higher in the corticosteroid group than in the control group (9 of 11 [82%] vs. 7 of 17 [41%]; P=0.05) (Figure 1). However, in patients with early AF recurrence, the rates in the corticosteroid and control groups were comparable (corticosteroid group, 7 of 11 [65%] vs. placebo group, 8 of 13 [62%], P=0.92) (Figure 1). In elderly patients over 60 years, the baseline characteristics, procedure and immediate (21% vs. 18%, P=0.79), early (6% vs. 13%, P=0.46) and late recurrence rates (17% vs. 10%, P=0.53) were not significant between the control and steroid groups. Overall, we were unable to detect a significant difference in the prevalence rates of AF recurrence between the corticosteroid group (13 [15%]) and the control group (26 [22%]; odds ratio 0.60, 95% confidence interval (CI) 0.29–1.25, P=0.21) without any AADs during the 12-month follow-up period. Furthermore, according to the type of AF, both the recurrence rate during and after 12 months were not different between the control and the corticosteroid groups (unpublished data). Figure 2 shows the Kaplan-Meier survival curves for AF recurrence. There was no difference in cumulative survival free of late AF recurrence between the corticosteroid and control groups (P=0.57 by log-rank test). By multivariate Cox-regression analysis, persistent AF (hazard ratio 2.87, 95% CI 1.33–6.20, P<0.01) was the only independent predictor of late recurrence after adjusting for use of steroid, diabetes mellitus, LA size and ablation time.

Discussion

The major finding of this study is that a single bolus injection of low-dose hydrocortisone did not prevent the recurrence of AF after RFCA. Second, the inflammatory makers CRP, WBC and BT did not change after treatment with low-dose hydrocortisone. Our study results suggest that at least a moderate dose of hydrocortisone is needed to prevent AF after RFCA.

Corticosteroids for Prevention of AF After Ablation

The use of corticosteroids for the prevention of AF has been mainly evaluated after cardiothoracic surgery.[18–21] Three independent meta-analyses have shown that therapy with corticosteroids is associated with a 26–58% reduction in relative risk of postoperative AF.[22–24] However, evidence supporting the use of steroids for the secondary prevention of AF after catheter ablation is extremely sparse. Recent studies have shown that increases in BT and CRP concentration from baseline in the immediate AF recurrence group (within 3 days after RFCA) were higher than in the early and no AF recurrence groups.[10,11] Consistent with this finding, Koyama et al[12] reported that the prevalence of immediate (≤3 days) and late (≥31 days) AF recurrence was significantly lower in the corticosteroid group than in the placebo group.[12] The early recurrence of AF has been reported as a significant predictor of long-term ablation failure.[25] Therefore, steroids may prevent long-term AF recurrence

in the same way that they prevent early recurrence of AF.

In this study, low-dose steroid did not change the incidence of AF recurrence in the patient group. However, interestingly, even low-dose hydrocorticosteroid (100 mg) seemed to be effective at preventing late AF recurrence in patients with immediate AF recurrence.

Efficacy and Dosage Effect of Corticosteroids for Prevention of Post-Ablation AF

There have been several studies of the dosage effect of corticosteroids for prevention of post-cardiothoracic surgery AF. Marik and Fromm analyzed 1,046 patients from 7 studies and classified the total cumulated dosage of corticosteroid as low (<200 mg/day), moderate (200–1,000 mg/day), high (1,001–10,000 mg/day), and very high (>10,000 mg/day) of hydrocortisone equivalents.[22] Overall, the use of perioperative corticosteroids reduces the risk of postoperative AF by greater than 50%. However, this effect appeared to be dependent on the dosing regimen used, with both very high and low dosages of corticosteroids being ineffective in contrast to the moderate- and high-dosage groups. Baker et al also reported that only the intermediate-dose group (50–210 mg of dexamethasone) had a significantly reduced incidence of post-cardiothoracic surgery AF versus placebo.[24] However, Ho et al reported that no additional benefits were found with all outcomes beyond a total dose of 1,000 mg hydrocortisone.[23] These data suggest that a cumulative dose of less than 200 mg or more than 1,000 mg of hydrocortisone is insufficient to adequately downregulate the systemic inflammatory response syndrome associated with cardiac surgery.[22]

There are no data indicating the optimal dose of corticosteroid required to suppress the inflammatory reaction after RFCA of AF. In an animal study,[26] a single, 500-mg methylprednisolone infusion did not change the CRP concentration or histopathological findings compared with control after biatrial linear ablation. However, Koyama et al reported that intravenous hydrocortisone (2 mg/kg) administered the day of the procedure and oral prednisone ($0.5\ mg \cdot kg^{-1} \cdot day^{-1}$) administered for 3 days after the PVI prevented AF.[12] Because the degree of inflammation after post-cardiothoracic surgery and RFCA differs, it is not adequate to use the same dosage of steroid after RFCA. However, our data strongly suggest that a low dose of less than 200 mg of hydrocortisone is insufficient to prevent post-ablation AF recurrence.

The mechanisms by which corticosteroids prevent postoperative AF are not entirely clear. The concentration of complement CRP complex,[27] the number of WBCs,[28] and the concentration of inflammatory cytokines,[29] all markers of increased inflammatory reaction, are higher in patients with postoperative AF than in patients who remain in sinus rhythm. Corticosteroids have antiinflammatory activity and reduce an exaggerated inflammatory reaction. In previous studies, the postoperative concentration of CRP was significantly lower in the corticosteroid group than in the placebo group.[12,21] However, low-dose steroid did not change WBC or CRP concentration or maximum BT in this study.

Study Limitations

The present study had several limitations. First, because this study was not a prospective randomized trial, there might be a selection bias in the use of steroid. However, we selected an age- and sex-matched control group, and there was no significant difference in the inflammatory markers, ablation procedure or baseline characteristics, including the echocardiographic parameters, between the steroid and control groups according to the type of AF. Although the patient selection depended on the operators, the experience, ablation protocol and procedural time was same for all the operators in this study. Second, continuous ECG monitoring was performed for the initial 2 hospital days. Because we used conventional ECG and ambulatory Holter monitoring, asymptomatic AF recurrence might not be included. Continuous recording for a longer period would have provided more insight into the effect of the steroid. Finally, the patients in this study were relatively younger (mean age, 55 years) than those usually encountered in clinical practice. Further study is needed to generalize this finding to patients with different ages.

Conclusions

Single bolus injection of low-dose hydrocortisone shortly after AF ablation is not effective for preventing immediate or early/late AF recurrence during the mid-term follow-up period after RFCA. Our study suggests that at least a moderate dose of hydrocortisone might be needed to prevent AF after RFCA. Further study will provide the dose information of corticosteroid for prevention of AF recurrence.

Acknowledgments

We thank Dong Wook Kim, PhD, and Hye Sun Lee, PhD for their statistical assistance.

Disclosure

This study was supported in part by faculty research grants from Yonsei University College of Medicine (6-2009-0176, 6-2010-0059, 7-2009-0583) and by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (2010-0021993).

Author Contributions: Dr Won analyzed and interpreted the data. Drs Kim, Shim and Uhm assisted the data analyses. Dr Won and Dr Joung drafted the manuscirpt. Dr Pak and Dr Lee critically revised the article. Dr Joung conceived and designed the research, and handled funding as well as the supervision.

References

1. Oral H, Knight BP, Ozaydin M, Tada H, Chugh A, Hassan S, et al. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. *J Am Coll Cardiol* 2002; **40:** 100–104.
2. Hagiwara N. Inflammation and atrial fibrillation. *Circ J* 2010; **74:** 246–247.
3. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: A systematic review of the published data. *J Am Coll Cardiol* 2007; **50:** 2021–2028.
4. Liakopoulos OJ, Schmitto JD, Kazmaier S, Brauer A, Quintel M, Schoendube FA, et al. Cardiopulmonary and systemic effects of methylprednisolone in patients undergoing cardiac surgery. *Ann Thorac Surg* 2007; **84:** 110–118; discussion 118–119.
5. Bourbon A, Vionnet M, Leprince P, Vaissier E, Copeland J, McDonagh P, et al. The effect of methylprednisolone treatment on the cardiopulmonary bypass-induced systemic inflammatory response. *Eur J Cardiothorac Surg* 2004; **26:** 932–938.
6. Kilger E, Weis F, Briegel J, Frey L, Goetz AE, Reuter D, et al. Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery. *Crit Care Med* 2003; **31:** 1068–1074.
7. Kourliouros A, Savelieva I, Kiotsekoglou A, Jahangiri M, Camm J. Current concepts in the pathogenesis of atrial fibrillation. *Am Heart J* 2009; **157:** 243–252.
8. Yamashita T, Sekiguchi A, Iwasaki YK, Date T, Sagara K, Tanabe H, et al. Recruitment of immune cells across atrial endocardium in human atrial fibrillation. *Circ J* 2010; **74:** 262–270.
9. Van Wagoner DR. Oxidative stress and inflammation in atrial fibrillation: Role in pathogenesis and potential as a therapeutic target. *J Cardiovasc Pharmacol* 2008; **52:** 306–313.
10. McCabe JM, Smith LM, Tseng ZH, Badhwar N, Lee BK, Lee RJ, et al. Protracted CRP elevation after atrial fibrillation ablation. *Pacing Clin Electrophysiol* 2008; **31:** 1146–1151.

11. Koyama T, Sekiguchi Y, Tada H, Arimoto T, Yamasaki H, Kuroki K, et al. Comparison of characteristics and significance of immediate versus early versus no recurrence of atrial fibrillation after catheter ablation. *Am J Cardiol* 2009; **103:** 1249–1254.
12. Koyama T, Tada H, Sekiguchi Y, Arimoto T, Yamasaki H, Kuroki K, et al. Prevention of atrial fibrillation recurrence with corticosteroids after radiofrequency catheter ablation: A randomized controlled trial. *J Am Coll Cardiol* 2010; **56:** 1463–1472.
13. Chiappini B, El Khoury G. Risk of atrial fibrillation with high-dose corticosteroids. *Expert Opin Drug Saf* 2006; **5:** 811–814.
14. Jahangiri M, Camm AJ. Do corticosteroids prevent atrial fibrillation after cardiac surgery? *Nat Clin Pract Cardiovasc Med* 2007; **4:** 592–593.
15. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010; **12:** 1360–1420.
16. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: Review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: Primary prevention. *Europace* 2011; **13:** 308–328.
17. Oral H, Chugh A, Lemola K, Cheung P, Hall B, Good E, et al. Noninducibility of atrial fibrillation as an end point of left atrial circumferential ablation for paroxysmal atrial fibrillation: A randomized study. *Circulation* 2004; **110:** 2797–2801.
18. Halvorsen P, Raeder J, White PF, Almdahl SM, Nordstrand K, Saatvedt K, et al. The effect of dexamethasone on side effects after coronary revascularization procedures. *Anesth Analg* 2003; **96:** 1578–1583, table of contents.
19. Prasongsukarn K, Abel JG, Jamieson WR, Cheung A, Russell JA, Walley KR, et al. The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: A prospective randomized trial. *J Thorac Cardiovasc Surg* 2005; **130:** 93–98.
20. Yared JP, Bakri MH, Erzurum SC, Moravec CS, Laskowski DM, Van Wagoner DR, et al. Effect of dexamethasone on atrial fibrillation after cardiac surgery: Prospective, randomized, double-blind, placebo-controlled trial. *J Cardiothorac Vasc Anesth* 2007; **21:** 68–75.
21. Halonen J, Halonen P, Jarvinen O, Taskinen P, Auvinen T, Tarkka M, et al. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A randomized controlled trial. *JAMA* 2007; **297:** 1562–1567.
22. Marik PE, Fromm R. The efficacy and dosage effect of corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A systematic review. *J Crit Care* 2009; **24:** 458–463.
23. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: A dose-response meta-analysis. *Circulation* 2009; **119:** 1853–1866.
24. Baker WL, White CM, Kluger J, Denowitz A, Konecny CP, Coleman CI. Effect of perioperative corticosteroid use on the incidence of postcardiothoracic surgery atrial fibrillation and length of stay. *Heart Rhythm* 2007; **4:** 461–468.
25. Richter B, Gwechenberger M, Socas A, Marx M, Gossinger HD. Frequency of recurrence of atrial fibrillation within 48 hours after ablation and its impact on long-term outcome. *Am J Cardiol* 2008; **101:** 843–847.
26. Nascimento T, Mota F, dos Santos LF, de Araujo S, Okada M, Franco M, et al. Impact of prophylactic corticosteroids on systemic inflammation after extensive atrial ablation in pigs. *Europace* 2012; **14:** 138–145.
27. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: Postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 1997; **96:** 3542–3548.
28. Lamm G, Auer J, Weber T, Berent R, Ng C, Eber B. Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. *J Cardiothorac Vasc Anesth* 2006; **20:** 51–56.
29. Ishida K, Kimura F, Imamaki M, Ishida A, Shimura H, Kohno H, et al. Relation of inflammatory cytokines to atrial fibrillation after off-pump coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2006; **29:** 501–505.