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Use of Oral Steroid and its Effects on Atrial Fibrillation Recurrence and Inflammatory Cytokines Post Ablation – The Steroid AF Study

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Abstract

Use of corticosteroids before and after atrial fibrillation (AF) ablation can decrease acute inflammation and reduce AF recurrence.To assess the efficacy of oral prednisone in improving the outcomes of pulmonary vein isolation with radiofrequency ablation and its effect on inflammatory cytokines, a total of 60 patients with paroxysmal AF undergoing radiofrequency ablation were randomized (1:1) to receive either 3 doses of 60 mg daily of oral prednisone or a placebo. Inflammatory cytokine levels (TNF-α, IL-1, IL6, IL-8) were measured at baseline, prior to ablation, immediately after ablation, and 24 hours post ablation. Patients underwent 30 day event monitoring at 3 months, 6 months and 12 months post procedure. Immediate post ablation levels of inflammatory cytokines were lower in the steroid group when compared to the placebo group; IL-6: 9.0 ±7 vs 15.8 ±13 p=0.031; IL-8: 10.5 ±9 vs 15.3 ±8; p=0.047 respectively. Acute PV reconnection rates during the procedure (7/23% vs 10/36%; p = 0.39), and RF ablation time (51±13 vs 56±11 min, p = 0.11) trended to be lower in the placebo group than the steroid group. There was no difference in the incidence of early recurrence of AF during the blanking period and freedom from AF off AAD at 12 months between both groups (5/17% vs 8/27%; p = 0.347 and 21/70% vs 18/60%; p=0.417 in placebo and steroid groups respectively).

CONCLUSION: Although oral corticosteroids have significant effect in lowering certain cytokines, it did not impact the clinical outcomes of AF ablation.

Introduction

Pulmonary vein isolation (PVI) is an effective treatment for symptomatic, drug refractory patients with paroxysmal atrial fibrillation (AF). Although the procedure decreases symptoms and AF burden in patients, the success rate of single procedure is only between 50%-75% [1]-[3] necessitating repeat procedures to improve the overall success rate.[4]-[9] Immediate post procedural atrial tissue inflammation can cause significant early recurrence of AF (ERAF). The long term recurrence of AF often is thought to be due to a persistent conduction gaps between the left atrium (LA) and pulmonary veins (PV).[10]-[13] The Inflammatory process associated with PVI can create significant local tissue edema resulting in transient loss of conduction in an area where permanent injury has not occurred. This can result in under ablation and subsequent reconnection of the PVs.

The anti-inflammatory effect of corticosteroids was studied extensively in cardiac surgery in the past. Corticosteroids have been shown to exert significant anti-inflammatory response as is evidenced by decreasing the levels of IL-6, IL-8, TNF, CRP, and oxygen free radicals after cardiac surgery .[10]-[13] Since the inception of our study, a few groups around the world have published data on the impact of steroids and AF ablation outcomes with significant variability. Koyama et al reported that the use of corticosteroid after AF ablation significantly decreases the immediate and late AF recurrence. However, 3 subsequent studies with different doses of IV corticosteroids found no effect in preventing early and late recurrence of AF .[3] [13]-[15] All of these studies attempted to understand the impact of only intra or post procedural steroid use. This approach may potentially suppress the immediate post ablation inflammation but may not have any impact on the intra-procedural reduction of tissue edema. We therefore attempted to study the impact of pre-treating at least 48 hours prior to the procedure to enable effective suppression of intra-procedural acute inflammatory response. This has not been addressed by any other study done so far. We aimed

Key Words

Atrial Fibrillation, Ablation, Pulmonary Vein Isolation, Interleukin, Tumor Necrosis Factor, Corticosteroid, Recurrence, Inflammatory cytokines, Prednisone.

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to systematically assess these effects through the measurement of inflammatory markers. The purpose of our study was to determine if the use of pre procedural corticosteroid can prevent early and late AF recurrence post ablation and evidence of reduction of inflammation through systemic cytokine assessment.

Methods

Study Population

We screened 105 patients of whom 60 patients with symptomatic drug refractory paroxysmal AF met inclusion and exclusion criteria and were enrolled in the study between September 2010 and November 2013. There were 30 patients in the steroid group and 30 patients in the placebo group. All patients were de novo AF ablation candidates. All patients failed at least 1 antiarrhythmic drug (AAD). AADs were discontinued 5 half-lives before the ablation procedure except for amiodarone. In those who were on AAD, it was continued for at least 8 weeks post ablation, and discontinued if no recurrence was found. The study was approved by the Institutional Review Board, and written consent was obtained from all participants. Patients were excluded due to history of corticosteroid use within 1 week of the study, use of non-steroidal anti- inflammatory drugs (NSAIDs), or colchicine within 1 week of the study,immunosuppressive disorders, chronic persistent AF, uncontrolled diabetes, or any other autoimmune disorders.

Table 1: Comparison of baseline characteristics, procedural variables and outcomes of atrial fibrillation after atrial fibrillation ablation between both the groups

Clinical characteristics	Placebo (n=30)	Corticosteroid (n=30)	p Value
Age	63 ± 8.9	63 ± 8.7	0.65
Body mass index	28.5 ± 5.2	30.5 ± 5.9	0.21
AF Duration (year)	6.9 ± 6.7	4.1 ± 4.1	0.059
LV Ejection Fraction (%)	56.2 ± 8.4	57 ± 4.7	0.70
LA Diameter (cm)	4.2 ±0.64	4.6 ±0.7	0.12
Procedure time (Minutes)	166 ± 47	174 ± 38	052
Male	22 (73)	24 (80)	0.76
Caucasian	26 (87)	26 (87)	1.0
Hypertension	12 (40)	18 (60)	0.19
Coronary Artery Disease	9 (30)	12 (40)	0.58
Valvular disease	13 (5.8)	11 (6.2)	2 (4.3)
COPD	1 (3.3)	2 (6.7)	1.0
Antiarrhythmic			
Class 1	8 (26.6)	4 (13.3)	0.33
Class 3	15 (50)	17 (56.7)	0.79
Medication			
Beta Blocker	13 (43)	12 (40)	1.0
Calcium channel blocker	7 (23)	6 (20)	1.0
Total Fluoroscopy Time (minutes)	54.8 ± 17.2	54.7 ± 16.5	0.9
Total RF tim (minutes)	51 ±13.5	56 ±10.7	0.11
Acute PV Reconnection rate	7 (23)	10 (36)	0.39
Early Recurrence (0-3 months); %	5 (17)	8 (27)	0.347
Recurrence after blanking period (3-12 months); %	9 (30)	12 (40)	0.417

Study design

This is a prospective, randomized, double-blinded study. All patients were randomized for treatment with corticosteroid (corticosteroid group), or a placebo (placebo group) 1 day prior, on the day of ablation and 1 day after the procedure with the help of the investigational pharmacy staff to blind and dispense the drug and the placebo.

Steroid Administration

In the corticosteroid group, 60 mg of oral prednisone was administered one day prior, on the day of procedure and one day after the procedure. An oral lactose pill was administered to the placebo group with the same schedule.

Adverse effect monitoring

Fasting glucose levels were performed on all patients. Glucose levels were checked before each meal and before bed in patient with diabetes mellitus (DM). Hyperglycemia was defined as fasting glucose >110 mg/dl and post prandial glucose >180 mg/dl. Patients were also monitored for signs of fluid retention and infection.

Monitoring of AF Recurrence

Patients were monitored on telemetry during hospitalization. After discharge, patients underwent 1 month event monitoring at 3 months, 6 months and at 12 months post procedure. Any episode of AF lasting more than 30 seconds was considered as recurrence. Recurrence of any atrial arrhythmias (atrial tachycardia (AT) or AF) at 3 months, 6 months, and 12 months post ablation was recorded for the assessment of endpoints.

Inflammatory Cytokines Monitoring

A blood sample (5 ml) from the antecubital vein was collected from all subjects at the time of before randomization which served as baseline sample. Blood samples were collected at the beginning and end of the ablation procedure and at 24 hour post ablation for cytokine measurement (IL1, 6, 8, and TNF α). All blood samples were centrifuged to collect serum and frozen at -70° C. Enzyme-linked immunosorbent assays (ELISA) were performed on the serum samples using kits (ELISA kit II, BD Bioscience, USA) for human-specific IL1 ρ (Cat. No: 557966), IL6 (Cat. No: 550799), IL8 (Cat. No: 550799) and TNF-α (Cat. No: 550610), according to the manufacturer's instructions.

Catheter Ablation and assessment of PVI

All patients underwent pre-procedural Cardiac CT to define the pulmonary vein anatomy and pre -procedural TEE to exclude thrombus. Three dimensional mapping of the LA was reconstructed with CARTO (Biosense Webster, Inc, Diamond Bar, CA, USA) or Velocity (SJM, Minneapolis, MN,USA) electroanatomic mapping system. PVI was performed using 3.5/4.0 mm irrigated tip catheter (Thermocool, Biosense Webster, Inc or Coolpath Flex, SJM) with a maximum temperature of 50 ° C and power output of 25-35 Watts using a roving Lasso technique at the antral level. A circular mapping catheter (Lasso, Biosense Webster, Inc) was used to confirm PVI. Bidirectional conduction block from the atrium to the PV and vice versa were confirmed. We performed induction testing using burst pacing or isoprotenolol and targeted if there were other non PV triggers only. If a patient had inducible right atrial flutter or a prior history of flutter, a cavo-tricuspid isthmus ablation was performed. No other lesions were allowed. Thirty minutes after the isolation of each PV, reconnection rates were assessed and re-ablated if necessary. Adenosine was not used for evaluation of dormant conduction. All patients had all PVs isolated at the end of the procedure.

Follow Up

Patient remained hospitalized under continuous rhythm monitoring for at least 24 hours after radiofrequency ablation (RFA) with subsequent follow up in 3 months, 6 months and 12 months. A 12-lead ECG was performed during every clinic visit with intensive

questioning regarding any arrhythmia related symptoms. Additionally patients underwent 30 day event monitors at 3, 6 and 12 months post-ablation. All patients remained on antiarrhythmic drugs for the first 2 months. In those who had symptomatic recurrences within the first 2 months, cardioversion was performed and/or AADs were changed; repeat ablation were performed if cardioversion and change in AAD did not alleviate AF symptoms.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables as proportions. Univariate analyses were performed using Chi-Square test (with or without Fisher's exact correction) for categorical variables and Student t-test for continuous variables. Paired tests were performed when appropriate. McNemar test was used for evaluating paired samples. Pre and post ablation inflammatory markers were compared using paired t-test. Statistical analysis was considered significant at p values ≤ 0.05. Statistical analysis was performed using SPSS version 23.0 (IBM Inc., USA). Binary logistic regression was used for multivariable analysis. All known variables impacting the recurrence of AF were entered into the multivariate model. A two sided p-value ≤0.05 was considered statistically significant.

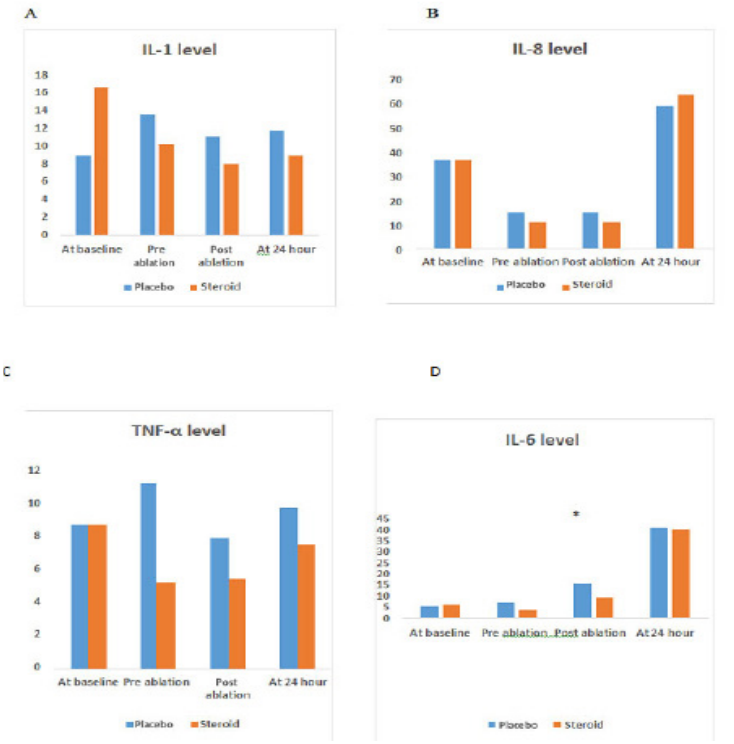

Figure 1: Comparison of inflammatory cytokines level at 4 different time points

Results

Study population

We screened a total of 105 patients of whom 60 patients met inclusion criteria and were subsequently randomized to receive prednisone or placebo.

Baseline and clinical Characteristics

Baseline characteristics are shown in [Table 1]. Both groups were comprised of 30 patients each. Baseline characteristics of mean age, gender, comorbidities, echocardiographic parameters, antiarrhythmic drugs and medications were not significantly different between the 2 groups.

Procedural Characteristics

Catheter ablation parameters and intra-procedural recurrences are presented in [Table 1]. PVI was successfully performed in all patients and bidirectional block was achieved in all PVs. The catheter ablation parameters were comparable between the 2 groups. Total procedure and fluoroscopic times were not different between them. Acute PV reconnection rates during the procedure (23% vs 36%; p=0.39), and RF ablation time (51 ±13 vs 56 ±11 mins, p = 0.11) were lower in the placebo group than the steroid group although not statistically significant.

Discussion

Major Findings

The main findings of our study are - 1) Oral prednisone during peri-procedural period did not impact the outcome of AF ablation. 2) The levels of inflammatory cytokines, specifically the IL-6 and IL-8 immediately post- ablation were significantly lower in the steroid group after ablation suggestive of effective suppression of systemic anti-inflammatory response by steroids.

Role of Steroid in AF Recurrence post Ablation

Previous Studies

There were no prospective clinical studies performed at the time of conception of this study. However, multiple studies were published since and have variable results. The role of steroids in preventing AF recurrence post ablation was first studied by Koyama et al in 2010 and showed decreased AF recurrence rate in the immediate (0-3 days) and during long term follow up (14 months). This study used 2mg/kg IV hydrocortisone on the day of procedure, followed by oral prednisolone (0.5 mg/kg/day) for 3 days. In addition, cavo-tricuspid isthmus ablation was done in all patients and additional ablation consisting of linear ablation of LA roof line and SVC isolation was performed if AF was induced with coronary sinus burst pacing and isoproterenol.[15] Later Won et al (2013) performed a similar study using low dose hydrocortisone (IV 100 mg) administered within 30 minutes post procedure with no difference in AF recurrence between steroid and placebo group. [13] Similarly, Andrade et al (2013) with 250 mg IV hydrocortisone immediately after transseptal puncture, Kim et al (2015) with low dose (100 mg IV hydrocortisone) and high dose (125 mg IV hydrocortisone) within 30 minutes post procedure did not show any difference in recurrence of AF. [14] Most of the clinical studies have been negative akin to our current study. This clearly points to the fact perhaps use of systemic corticosteroids and suppression of inflammation has no definitive impact on clinical outcomes in AF ablation.

Type and timing of Steroid Administration

The major difference between our study and the previous 4 studies described above was the timing of steroid administration and the type of steroid used. Prednisone has a half-life of 12-36 hours and it has 5 times more glucocorticoid potency than hydrocortisone. Based on pharmacologic properties (See [Figure 2]), we chose prednisone which is an intermediate acting steroid and administered 3 doses prior to ablation to maximize the anti-inflammatory effect and prevent tissue edema which was thought to contribute to gaps in PV isolation. The 60 mg prednisone is equivalent to 300 mg IV hydrocortisone which has half-life of 8-12 hours. Contrary to our hypothesis, this strategy did not show any efficacy in preventing AF recurrence. Our study is in agreement with 3 previous studies.

Positive effects reported by Koyama et al may be due to prolonged post procedural steroid therapy and possible suppression of regional and systemic inflammation in the setting of more aggressive ablation. [13]

Steroids and AF Recurrence

Although not statistically significant, our study found a trend towards higher recurrence rate in the steroid group. Studies have shown that acute administration of hydrocortisone can result in rapid concentration dependent cellular hyperpolarization in neural and cardiac tissue. [3,16-18] This hyperpolarization is thought to counteract RF induced membrane depolarization in the surrounding tissue requiring prolonged ablation time and higher probability of conduction gaps or acute reconnections. [19]

Table 2: Corticosteroid Comparison Chart

Drug	Equivalent dose (mg)	Glucocorticoid Potency	mineralocorticoid potency
Prednisone	5	4	0.8
Methylprednisolone (solumedrol)	4	5	0.5
prednisolone (medrol)	5	4	0.8
Hydrocortisone (solucotef)	25	1	1
Dexamethasone (decadron)	0.75	25	0
fludrocortisone (Florinef)	N/A	10	125

Drug	Plasma Half-ilfe	Biologic Half-life
Prednisone	160 min	12-36 hrs
Methylprednisolone (solumedrol)	80-180 min	12-36 hrs
prednisolone (medrol)	115-250 min	12-36 hrs
Hydrocortisone (solucotef)	80-115 min	8-12 hrs
Dexamethasone (decadron)	110-120 min	36-72 hrs
fludrocortisone (Florinef)		

Effects of Steroid on Pulmonary Reconnection Rates and Radiofrequency time

Similar to study by Andrade et al, our study shows trend towards higher RF time and PV reconnection rate. Interestinglystudy by Andrade et al shows those pre-procedural steroids are associated with higher prevalence of dormant conduction and increased RF ablation time to accomplish PV isolation.[3] In addition, two large population based case control study found an increase risk if AF during current use [20] or high dose [21] regimen of corticosteroid therapy.[22] Perhaps steroid inhibits effective scar formation from the ablation lesions. As a result of which partially injured atrial tissue has a higher propensity to recover due to the effect of the steroids and result in non-durable PV isolation.

Inflammatory Cytokines and AF Recurrence

Our study showed a significantly lower IL-6 and IL-8 post procedure in the steroid group which reflected the anti-inflammatory effect of steroid, however, they was no association between these cytokine changes and AF recurrence. There is uncertainty whether the inflammation from ablation promotes AF, or if the inflammation is caused by the arrhythmia itself or both. Previous studies have shown CRP elevation after RFA which correlated with early arrhythmia recurrence suggesting that extensive tissue damage from ablation may be pro inflammatory. [23]-[25] However, animal studies by Nascimento et al using young healthy pigs without arrhythmia that was divided in to placebo, sham ablation, and ablation with 500 mg IV methylprednisolone showed no difference in CRP level and similar histological findings in all 3 groups suggestive of extensive tissue damage due to ablation suggesting that RF energy per se was not responsible for systemic inflammation and the rise in CRP was rather related to procedural stress.[25]

Study Limitation

It is a relatively small study with all the obvious limitations. We also realize that our study was probably underpowered to detect a difference in outcomes between the groups. However, this was a randomized double blind placebo control study with relevant inflammatory markers measured at various time lines clearly establishing the linear relationship between steroid use and anti-inflammatory effects. We did not measure CRP levels as we deemed it to be too non-specific and has not been shown to be very useful in the previous studies.

Conclusion

Use of oral corticosteroids resulted in significant anti-inflammatory effect as evidenced by reduction in inflammatory cytokine levels with no impact on the clinical outcomes of AF ablation. There is a trend towards higher incidence of AF recurrence, higher PV reconnection rate, and longer RF ablation time with administration of steroids.

Conflict Of Interests

None.

Disclosures

None.

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