

# Use of short-term steroids in the prophylaxis of atrial fibrillation after cardiac surgery



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**Objectives:** To assess the effectiveness of corticosteroids in the prophylaxis of postoperative atrial fibrillation (AF) in patients undergoing elective coronary artery bypass grafting or valvular heart surgery in terms of reducing its incidence and decreasing the length of hospital stay.

**Methods:** This prospective double blinded randomized study was conducted at Queen Alia Heart Institute (Amman, Jordan) from June 2014 to June 2015 on 340 patients who underwent their first on-pump elective coronary artery bypass grafting (CABG) alone or combined with valvular surgery. Inclusion criteria consisted of elective first time CABG or combined with valvular surgery, use of  $\beta$ -adrenergic blockade, and normal sinus rhythm. Exclusion criteria included a history of heart block, previous episodes of AF or flutter, uncontrolled diabetes mellitus, history of peptic ulcer disease, systemic bacterial or mycotic infection, permanent pacemaker, and any documented or suspected supraventricular or ventricular arrhythmias. Patients were randomized into two equal groups ( $n = 170$  each), then each group was subdivided into patients who underwent CABG alone ( $n = 120$ ), and patients underwent valvular heart surgery with or without CABG ( $n = 50$ ). In the treatment group, patients were given 1 g of methylprednisolone before cardiopulmonary bypass then 100 mg of hydrocortisone every 8 hours for the first 3 days postoperatively. The primary endpoint was the overall occurrence of postoperative AF.

**Results:** AF developed in 21.1% (36 patients) in the treatment group in contrast to 38.2% (65 patients) in the control group ( $p < 0.05$ ). In the subdivided groups (CABG only), approximately 20% (24 patients) developed AF in the treatment group in contrast to 35% (42 patients) in the control group ( $p < 0.05$ ). In the other group, (CABG + VALVE) 24% (12 patients) developed AF compared with 46% (23 patients) in the control group ( $p < 0.05$ ). The length of hospital stay was 6.02  $\pm$  11.23 days in the treatment group while it was 5.98  $\pm$  1.86 days in the control group, which was found to be statistically nonsignificant. No statistical significant difference in the rate of postoperative complications including mediastinitis as well superficial wound infections was observed between the two groups.

**Conclusion:** Prophylactic short-term use of steroids both intraoperatively and postoperatively proved to be safe and effective in reducing the incidence of postoperative AF in patients undergoing CABG alone or combined with valve surgery.

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## Introduction

Coronary artery bypass grafting (CABG) using cardiopulmonary bypass triggers generalized response characterized by leukocyte and complement activation, high levels of C-reactive protein (CRP) complexes, as well high levels of inflammatory mediators [1–3]. These mediators, such as interleukins-6 and -8, tumor necrosis factors, leukotriene B4, and tissue plasminogen activator, might contribute to many postoperative complications including atrial fibrillation (AF), myocardial ischemia, multiorgan dysfunction, and infections [1–4]. This is because those substances have known cardiodepressant effects [5].

AF is the most common postoperative complication with incidence of 20–50% following CABG [1,3] and even higher after CABG and valve surgery in up to 40–50% [1]. It commonly occurs at 0–4 days [6,7] with the peak incidence on the 2<sup>nd</sup> to 3<sup>rd</sup> postoperative day [7–9]. AF is associated with hemodynamic instability, increased risk of thromboembolism and stroke, prolonged hospitalization and increased morbidity with consequent high costs [1,2,10,11].

Many drugs have been used to decrease the likelihood of developing AF, including  $\beta$ -adrenergic blockers, amiodarone, and magnesium [3,12].

Because of the known physiologic effects of steroids to suppress the release of the above mentioned inflammatory mediators, steroids might have beneficial effects in decreasing postoperative AF, and inhibiting the inflammatory process post-cardiopulmonary bypass [1,3,5]. Moreover, they decrease capillary wall permeability, preventing migration of inflammatory mediators into the systemic circulation [5]. However, much debate exists regarding their protective effects in relation to the well-known side effects such as hyperglycemia, gastrointestinal disturbances, and postoperative infection [1,5].

The purpose of this study is to assess the use of short-term steroids in the prophylaxis of AF in patients undergoing elective CABG or combined CABG and valvular heart surgery.

## Methods

This was a prospective randomized controlled study that was conducted at Queen Alia Heart Institute (Amman, Jordan) between June 2014 and June 2015. The study protocol was approved by the Jordanian royal medical services local

### Abbreviations

AF	atrial fibrillation
CABG	coronary artery bypass grafting
CPB	cardiopulmonary bypass
LA	left atrium
GIT	gastrointestinal
CRP	creactive protien
COPD	chronic obstructive lung disease
RCTs	randomized controlled trials

ethical committee. There were 340 consecutive patients scheduled to undergo their first on-pump CABG, or combined CABG and valvular surgery enrolled in this study. A total of 865 patients were screened with 516 excluded from the study as well nine patients who refused to be enrolled in the study.

Inclusion criteria consisted of elective first time CABG or combined with valvular surgery, use of  $\beta$ -adrenergic blockade, and normal sinus rhythm. Exclusion criteria included: a history of heart block; previous episodes of AF or flutter; uncontrolled diabetes mellitus; history of peptic ulcer disease; systemic bacterial or mycotic infection; permanent pacemaker; any documented or suspected supraventricular or ventricular arrhythmias; urgent or emergency surgery; if the patient underwent cardiac surgery without using cardiopulmonary bypass; and renal insufficiency (serum creatinine >20 mg/dL).

The study's primary end point was the occurrence of an episode of AF lasting  $\geq 30$  minutes or hemodynamic instability due to AF regardless of episode duration during the first 96 hours after cardiac surgery. Secondary end points were the length of hospital stay and the adverse effects of steroids. We followed up the patients during the first 2–4 weeks after surgery to check for wound infection, therefore, patient charts were ordered for verification. In addition, the patient charts were checked 6 months after the surgery to assess the incidence of major postoperative complications (mediastinitis or other complications requiring hospitalizations).

All patients in the hydrocortisone and placebo groups underwent the complete protocol of the intended treatments until designated end points, so intention was the same as treatment. After the first episode of AF, the study protocol was discontinued.

Patients underwent cardiac surgery on standard cardiopulmonary bypass. Intermittent blood or cold cardioplegia solution was administered via the antegrade or retrograde route. The cardioplegia solution consisted of 32 meq/dL of magnesium

and no extra magnesium substitution was administered. No steroids were included in the perfusion protocol.

The age, history of hypertension or diabetes mellitus, total pump time and aortic cross clamp time, time onset of AF, and hospital stay duration were recorded. The protocol was double-blinded, 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.

Randomization lists were sent to the department of pharmacy, where study drugs were prepared. The investigator sent the name and date of birth each time a new patient had given written informed consent. Randomization was performed on the operation day. The pharmacist selected the next number on the randomization list, labelled the drug container with the patient's name, and sent the container to the department where the patient was treated. The study group remained unknown to all caring nurses and physicians. The randomization codes were opened after the end of study. The study drugs were prepared in our center's department of pharmacy under aseptic technique. Both the active drug and the placebo preparations were identical regarding color and other characteristics.

All patients who were randomized into either the study or control group, had normal sinus rhythm prior to surgery.

Patients were divided into two major equal groups, each including 170 patients: i.e., the steroid group and the saline (control) group. Then each group was subdivided into patients undergoing isolated CABG ( $n = 120$ ), and patients undergoing valve surgery with or without CABG ( $n = 50$ ).

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 methyl prednisolone sodium succinate before cardiopulmonary bypass, and then 100 mg hydrocortisone every 8 hours for the next 3 days. Patients received the usual postoperative cardiac care including  $\beta$  blockade to prevent atrial arrhythmias.

Patients stopped receiving either choice if AF occurred. Regarding general anesthesia, surgical techniques and patient monitoring were standardized for all patients.

Patients were continuously monitored in the cardiac surgery intensive care unit with arterial and central venous monitoring. Cardiac rhythm was continuously monitored in the intensive care unit using bed side monitors and telemetry in the ward. The ward monitors stored 24-hour electrocardiographic recordings for subsequent analysis and 12 lead electrocardiographic recordings were performed if necessary to confirm the rhythm.

Values are presented as means  $\pm$  standard deviation and percentages. Chi-square was used to analyze the results, differences were considered to be statistically significant when  $p < 0.05$ . The test was used for comparison of patients in terms of duration of hospitalization.

## Results

The demographic data did not differ significantly between the two groups as the groups were well matched.

The age of the treatment and control group were comparable ( $64.2 \pm 8.9$  years vs.  $65.7 \pm 9.2$  years) as was the sex (52.3% men vs. 50.5% men). Hypertension was found in 54.7% (93 patients) of the placebo group and in 52.3% (89 patients) of the treatment group. Diabetes was found in 31.1% (53 patients) of the placebo group and in 32.3% (55 patients) of the treatment group. No statistical significance was found between the two groups in

Table 1. Characteristics of the patient groups.

Characteristics	Placebo ( $n = 170$ )	Hydrocortisone ( $n = 170$ )	Univariate $p$
Age (y)	$64.2 \pm 8.9$	$65.7 \pm 9.2$	NS
Male	89 (52.3)	86 (50.5)	NS
Female	81 (47.7)	84 (49.5)	NS
Hypertension	93 (54.7)	89 (52.3)	NS
Diabetes	53 (31.1)	55 (32.3)	NS
History of COPD	11 (6.4)	13 (7.6)	NS
Preoperative use of $\beta$ -blockers	141 (82.9)	147 (87)	NS
Unstable angina	33 (19.4)	35 (20.5)	NS

Data are presented as  $n$  (%) or mean  $\pm$  SD.

COPD = chronic obstructive pulmonary disease; NS = not significant; SD = standard deviation.

Table 2. Perioperative characteristics of the patient groups.

Characteristics	Placebo (n = 170)	Hydrocortisone (n = 170)	Univariate p
Type of surgery			
Isolated CABG	120 (70.5)	120 (70.5)	
Combined CABG and valve	50 (29.5)	50 (29.5)	
Total pump time (min)	102.5 ± 22.32	103.6 ± 21.85	NS
Aortic cross clamp (min)	55.62 ± 13.82	54.82 ± 14.20	NS
Development of atrial fibrillation	65 (38.2)	36 (21.17)	< 0.001
CABG group (n = 120)	42 (35)	24 (20)	< 0.05
CABG + valve (n = 50)	23 (46)	12 (24)	< 0.05

Data are presented as n (%) or mean ± SD.

CABG = coronary artery bypass graft; NS = not significant; SD = standard deviation.

the preoperative use of  $\beta$ -blockers or history of chronic obstructive pulmonary disease. Preoperative characteristics are shown in Table 1.

Mean aortic cross clamp time in the placebo group was 55.62 ± 13.82 minutes versus 54.82 ± 14.20 minutes in the treatment group. The total pump time was found to be 102.5 ± 22.32 minutes in the placebo group versus 103.6 ± 21.85 minutes in the treatment group. Both parameters were found to be statistically nonsignificant ( $p > 0.05$ ; Table 2).

The incidence of postoperative AF was found to be 21.17% in the hydrocortisone group (36 patient developed AF) versus 38.2% (65 patients developed AF) in the placebo group (Fig. 1).

When dividing the patients into those who underwent CABG only and those who underwent

valve surgery with or without CABG, the incidence of AF in the CABG group was 20% (24 patients) in the hydrocortisone group while it was 35% (42 patients) in the placebo group ( $p < 0.05$ ). By contrast, in the CABG and valve group the incidence of AF in the hydrocortisone group was 24% (12 patients) in comparison to 46% (23 patients) in the placebo group ( $p < 0.05$ ). It was seen that the incidence of AF was higher in the valve patients than the CABG group with or without hydrocortisone treatment, which is due partly to the effect of valve pathology.

Serum potassium and magnesium levels were not found to be statistically significant between the two groups, which excludes any electrolyte disturbances as potential cause for the significance difference in development of AF. However,

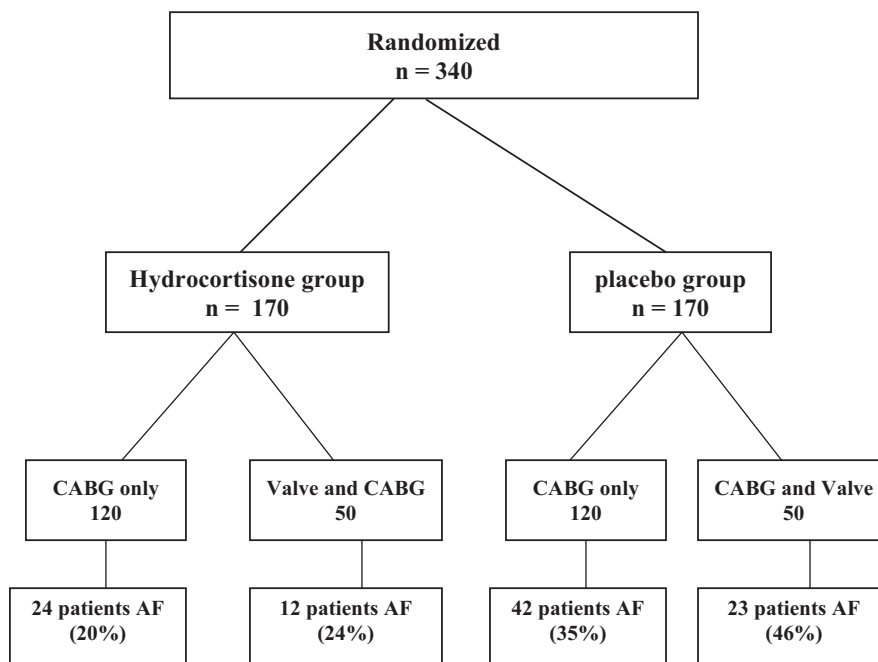


Figure 1. Summary of the study results. AF = atrial fibrillation; CABG = coronary artery bypass graft.

Table 3. Postoperative characteristics of the patient groups.

Characteristics	Placebo (n = 170)	Hydrocortisone (n = 170)	Univariate p
Onset of AF (h after operation)	22.4 ± 23.5	18 ± 22.6	NS
In hospital AF	65 (38.2)	36 (21.17)	< 0.001
Mortality during study period	2 (1.17)	2 (1.17)	NS
Perioperative MI	3 (1.76)	2 (1.17)	NS
Upper GIT bleeding	6 (3.5)	7 (4.1)	NS
Postoperative mediastinitis	2 (1.17)	3 (1.76)	NS
Superficial wound infection	9 (5.29)	11 (6.4)	NS
High blood sugar	7 (4.1)	13 (7.6)	NS
Serum potassium level before AF (meq/L)	4.3 ± 0.29	4.2 ± 0.35	NS
Serum magnesium level before AF (meq/dL)	1.7 ± 0.32	1.8 ± 0.29	NS
Postoperative CRP level (mg/L)			
1 <sup>st</sup> day	65.1 ± 28.2	51.1 ± 24.8	< 0.05
2 <sup>nd</sup> day	171.2 ± 45.2	102.3 ± 35.2	< 0.05
3 <sup>rd</sup> day	183.2 ± 50.2	97.2 ± 40.2	< 0.05
Length of hospital stay (d)	5.95 ± 1.95	6.02 ± 2.25	NS
Left atrial chamber size (units)	4.5 ± 1.7	4.7 ± 1.6	NS

Data are presented as n (%) or mean ± SD.

AF = atrial fibrillation; CRP = C-reactive protein; GIT = gastrointestinal; MI = myocardial infarction; NS = not significant; SD = standard deviation.

the concentration of CRP on the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> postoperative days were significantly lower in the hydrocortisone group than in the placebo group (Table 3) which might explain the anti-inflammatory effects of steroids on patients post-cardiopulmonary bypass. No statistical difference was found in left atrium (LA) size between the two groups, which exclude this factor as potential cause for increased risk of developing AF.

There were no statistically significant differences between the two groups with respect to mediastinitis, superficial wound infections, upper gastrointestinal bleeding, and overall mortality. However, it was noticed that blood sugar levels were higher in the hydrocortisone group, but with no statistical significance.

With regard to the distribution of valvular operations performed, aortic valve replacement is the commonest followed by mitral valve replacement (see Table 4).

Table 4. Distribution of operations performed.

Type of surgery	n	Percentage (%)
CABG + AVR	5	10
AVR	14	28
MVR	11	22
CABG + MVR	6	12
AVR + MVR	5	10%
MVR + TVR	7	14%
AVR + MVR + TVR	2	4%

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; TVR = tricuspid valve repair.

## Discussion

Prophylactic short-term steroids given in patients undergoing CABG reduced the occurrence of postoperative AF by approximately 50% [3]. In our study, it was found to be approximately 45% decreased risk of developing AF in patients undergoing isolated CABG and CABG combined with valve surgery, which is close to the landmark work of Halonen et al. [2], who conducted a prospective, double-blind, randomized multicenter trial of the effect of 100 mg hydrocortisone given intravenously every 8 hours for 3 days post-operatively. They found 37% risk reduction in the development of AF in the group who received hydrocortisone compared with the control group. In this study, the incidence of AF was significantly lower in the hydrocortisone group (30% vs. 48%; p = 0.004).

The mechanism behind the beneficial effects of hydrocortisone on the development of AF is not well known [2]. Direct effects of steroids, such as reduction in proinflammatory cytokine release, slowed leukocyte migration, and decreased capillary leak have been proposed as possible mechanisms [3,13–16]. Moreover, Halonen et al. [2] found a significant decrease in CRP levels in the group who received hydrocortisone. Hence, this might support the inflammatory etiology of post-operative AF. A study by Dernellis and Panaretou [17] also found that corticosteroid therapy reduces the CRP values and the risk of recurrent and permanent AF in nonoperative patients. Another possible effect of steroids is the antiemetic effect with

consequent improvement in absorption of oral medications such as  $\beta$ -blockers with resulting reduction in the incidence of AF [2].

Concerning the risk analysis of postoperative AF, we found that the older age group, chronic obstructive pulmonary disease patients, male sex, valve surgery, and longer cross clamp time, were significant predictors of AF development. After adjusting the above-mentioned factors, corticosteroid administration was found to be a significant independent predictor of absence of AF.

Yared et al. [18] found the same result of a lower incidence of new-onset AF with the administration of dexamethasone 0.6 mg/kg after induction of anesthesia. They found that patients receiving dexamethasone had a lower incidence of AF during the first 3 days postoperatively (18.9% vs. 32.3%;  $p = 0.02$ ). Prasongsukarn et al. [3] enrolled 88 patients in their randomized controlled study (43 patients received 1 mg of methylprednisolone before surgery and 4 mg of dexamethasone every 6 hours for 1 day after surgery). They found that AF occurred in 9 (21%) patients in the steroid group and 22 (51%) patients in the placebo group ( $p = 0.003$ ).

Ho and Tan [19] analyzed 50 randomized controlled trials including 3323 patients and found that corticosteroids prophylaxis reduced the risk of postoperative AF (25.1% vs. 35.1%). With regard to the dose-related effects of hydrocortisone on postoperative AF, Marik and Fromm [20] found that moderate doses of hydrocortisone equivalents (200–1000 mg/d) should be considered for the prevention of AF in high risk patients undergoing cardiac surgery. Furthermore, Ho and Tan [19] found that low-dose corticosteroid is as effective as high-dose corticosteroid in reducing the risk of AF and mechanical ventilation but with fewer potential side effects in adult cardiac surgery; i.e., no additional benefits were found on all outcomes beyond a total dose of 1000 mg hydrocortisone. Nevertheless, the study by Halvorsen et al. [21] showed that dexamethasone (4 mg of dexamethasone or placebo after induction of anesthesia and on the 1<sup>st</sup> postoperative day in 300 patients undergoing CABG) was beneficial in reducing emetic symptoms and improving appetite after cardiac surgery but had no effect on the occurrence of postoperative AF. This may be related to the different doses of corticosteroids used in each study [3], as well as the duration of corticosteroid administration so as to cover the days with peak AF development (2<sup>nd</sup> day and 3<sup>rd</sup> day).

Increased likelihood of wound infections and gastrointestinal bleeding (stress ulcer) is a concern

with the use of steroids. In our study, there was no statistical difference in the rate of major complications between the steroid and the placebo groups. Wound infection, whether deep or superficial, did not increase significantly upon using steroids. Also, both groups had a similar rate of upper gastrointestinal bleeding. In the study by Prasongsukran et al. [3], there was no statistically significant difference in major and overall complications between the steroid and placebo groups, although there was statistically significant difference in minor complications between the two groups. High blood sugar levels as well as impaired glucose tolerance were seen more in the steroid group, which was also noticed in our study but with no statistical significance. The Cochrane analysis [22] did not find an increased risk of infection in 15 studies including infectious complications as secondary outcome. Ali-Hassan-Sayegh et al. [1] found in a meta-analysis of 23 randomized controlled trials (RCTs) that corticosteroid therapy did not increase incidence of postoperative infection with an odds ratio of 1.03 (95% confidence interval: 0.68–1.5;  $p = 0.8$ ) with all doses (low, medium, high). In addition, they found in a meta-analysis of 11 randomized controlled trials that corticosteroid therapy did not have the ability to reduce the incidence of postoperative myocardial infarction [1], which is similar to the results found in our study.

Regarding the length of hospital stay, no statistically significant difference was found between the treatment and control groups, which was also seen in other studies [3]. Length of hospital stay has been investigated in three meta-analyses [1,22,23]. The Cochrane meta-analysis [22] found significant reductions in hospital stay by about half a day (95% confidence interval, 0.65–0.15). The results of the three meta-analyses are similar, and they all had significant heterogeneity between studies as a result of different time-span coverage as well as different corticosteroid dose regimens in different risk categories of patients [5]. Ali-Hassan-Sayegh et al. [1] found in a meta-analysis of 35 trials that corticosteroid therapy could significantly reduce length of hospital stay.

Regarding gastrointestinal complications, since 1990 only three small studies involving a total of 204 patients have gastrointestinal bleeding as secondary outcome [3]. In the Cochrane meta-analysis [22], these three studies showed a trend of increased gastrointestinal bleeding in the corticosteroid group although significant heterogeneity exists between the studies [5].

### Limitation of study

Although our study showed obvious beneficial effects of steroids in reducing postoperative AF, we noticed a slight increase in postoperative complications with no statistical significance. Therefore, our study was underpowered to assess the safety of corticosteroids, which makes it essential to undertake a larger trial to demonstrate the superiority of corticosteroid treatment compared with placebo in different doses. In fact, we encountered obvious difficulties in including other centers in the study due to the small number of cases done there in addition to technical problems. Furthermore, we should adjust the corticosteroid doses (e.g., give half the dose of methylprednisolone, 500 mg, instead of 1 g) and more importantly use steroids for selective patients, who are at higher risk of developing AF, such as chronic obstructive pulmonary disease, older patients, valvular disease, and longer cross clamp surgeries. Moreover, we can avoid diabetic patients, especially those with uncontrolled blood sugar, who are potentially at risk of infections. Further studies are needed to show the benefits of combining steroids with other preventive measures (such as intravenous amiodarone and magnesium) in reducing the risk of postoperative AF after cardiac surgery.

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