

# Effect of Prophylactic Low Dose of Methylprednisolone on Postoperative New Atrial Fibrillation and Early Complications in Patients with Severe LV Dysfunction Undergoing Elective Off-Pump Coronary Artery Bypass Surgery

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**Abstract-** Atrial fibrillation (AF) is the most common arrhythmia after cardiothoracic surgery. AF following coronary artery bypass graft (CABG) is associated with an increase in morbidity, mortality, hemodynamic instability, thromboembolic events, severity of heart failure and ICU and hospital stay. Corticosteroids have a variety of beneficial effects on recovery after elective surgery. This study was designed to test the hypothesis that low dose of Methylprednisolone (MP) can affect post-CABG AF and early complications in patients with severe left ventricle dysfunction who underwent elective off-pump coronary artery bypass. A total of 120 patients with LV dysfunction undergoing elective off-pump CABG randomly received either MP or placebo. Diabetic patients and those who were receiving corticosteroids were excluded. The MP group received 5mg/kg of MP intravenously after induction of anesthesia and the placebo group received an equal volume of normal saline. We evaluated Post-CABG variables including incidence, duration and frequency of AF recurrence and early morbidity such as bleeding, infection, vomiting, renal and respiratory dysfunctions, ICU or hospital stay and early mortality. The mean age of patients was  $62.11 \pm 12.34$  years with the 2.4 male to female ratio. AF occurred in 23(19.2%) patients. No significant difference in the incidence of new AF was found between the placebo (21.7%) and MP group (16.7%) ( $P=0.47$ ). MP did not affect postoperative bleeding, infection, vomiting, renal and respiratory dysfunction and mortality; however, MP significantly reduced ICU and hospital length of stay. MP did not affect the incidence, duration and frequency of AF recurrence in patients with severe LV dysfunction undergoing off-pump CABG. However, MP could reduce ICU and hospital stay significantly in these patients.

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**Keyword:** Methylprednisolone; Atrial fibrillation; Ventricular dysfunction, left; Coronary artery bypass

## Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia after coronary artery bypass graft (CABG) surgery. Incidence of AF has been reported in 20%-50% of patients following CABG surgery and is even higher after combined CABG and valve surgery. It occurs on the second or third day after operation (1-4). The factors important in producing postoperative AF are of the followings: age, male sex, BMI>30, right coronary graft failure, preoperative leukocytosis, low ejection fraction, atrial dilatation, long-term aortic cross clamp, increase

in plasma level of inflammatory markers and postoperative pericarditis (3,4). Postoperative atrial fibrillation (POAF) can increase stroke, hypertension, pulmonary edema, heart failure, hemodynamic instability, thrombolytic events, kidney and respiratory disorders, longer stay in ICU and hospital as well as increase in therapy costs (5,6). Complement and C-reactive protein complex levels as main markers of inflammatory reaction increase in patients who develop AF. This inflammatory reaction may contribute to the development of postoperative complications such as myocardial injury and multiple organ failure (7,8).

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Corticosteroids have some beneficial effects on recovery after elective surgery. However, there is controversy surrounding their anti-arrhythmic effects. They also have some side-effects such as hyperglycemia, gastrointestinal disturbances, dysphoria and psychotic reaction (9,10). According to probable complications of corticosteroids on patients experiencing cardiac surgery, we decided to use low dose of a weak steroid such as Methylprednisolone (MP) for high risk patients undergoing off-pump CABG who suffered from severe left ventricle (LV) dysfunction. This study was designed to evaluate the effect of preoperative low dose of MP on POAF and early complications after off-pump CABG surgery in patients with severe LV dysfunction.

## Material and Method

Our study was approved by regional committee in our university. After receiving the informed written consent from patients (n=120) with severe LV dysfunction, they participated voluntarily for off-pump CABG surgery in Afshar Cardiovascular Center of Yazd from 13 November 2009 to 20 December 2010. All the operations were performed by a certain surgical team. The patients receiving chronic corticosteroid and those with diabetes mellitus and a history of cardiac arrhythmia were excluded from the study. The patients were randomly assigned into two groups; the experimental group that received 5mg/kg of MP intravenously after induction of anesthesia and the placebo group that received an equal volume of normal saline. After adequate exposure and stabilization, the target vessel was exposed and snared above the anastomosed site with a 4-0 prolene suture and a soft plastic snigger to prevent coronary injury. The coronary artery was then opened and anastomosis was performed. Visualization was enhanced by utilizing surgical blower-humidifier and coronary artery shunt support. As premedication, all the patients received oral diazepam (10mg) 30-60 minutes before introduction into the operating room. Induction of anesthesia was performed

through diazepam (20mg), fentanyl (10-15 $\mu$ g/kg) and pancuronium (0.1mg/kg). For maintaining the anesthetic state, fentanyl (4-5 $\mu$ g/kg/h) and pancuronium (0.3-0.4mg/kg/h) were used. The drug used for this study (either MP 5mg/kg or saline) were injected intravenously after induction of anesthesia and before incision into the skin. The demographic variables and early postoperative complications such as infection, bleeding, vomiting, heart failure, renal and respiratory dysfunction, ICU and hospital stay were recorded. The individual who recorded the data did not know about the patients' groups. All patients underwent holter monitoring after ICU discharge during their hospital stay. Our data were analyzed by SPSS 15 software. We used ANOVA, Chi-Square and Fisher exact test for quantitative and qualitative variables.

## Results

120 patients with severe LV dysfunction enrolled in this study as possible candidates for CABG surgery. Of those, 85 cases (70.8%) were male and 55(29.2%) were female. The demographic characteristics of our patients have been presented in Table 1. Of all the participants, AF was observed in 23 patients (19.2%), 15 of whom were male (17.6%) and 8 were female (22.9%). There was not a significant relationship between sex and AF after surgery. The patients were divided into two age groups; less than 60 years old with the age average of 52 $\pm$ 3 and above 60 years old with the age average of 65 $\pm$ 4. POAF occurred in 5 cases (10%) out of 50 with less than 60 years of age while this occurred in 18 cases (25.7%) out of 70 equal or over 60 years. There was a direct relationship between increase in AF and age. In our patients the significant stenosis of one, two, three and left main vessel disease were 8 cases (6.7%), 32 cases (26.7%), 68 cases (57.6%) and 12 cases (10%) respectively. There were 2 cases (25%) of AF with one vessel, 4 cases (6.3%) with two vessels, 14 cases (20.6%) with three vessels and 5 cases (41.77%) of AF in those patients suffering from left main artery disease.

**Table 1.** Preoperative demographic characteristics of both groups

Variables	Control Group	Methylprednisolone Group	P-value
Age(year)	61 $\pm$ 13	63 $\pm$ 11	0.40
Sex(M/F)(n)	41 / 19	44 / 16	0.24
HTN [n (%)]	21 (35)	31 (51.7)	0.09
HLP [n (%)]	15 (25)	16 (26.7)	0.44
Cigarette smoking [n (%)]	16 (26.7)	8 (13.3)	0.12
Addiction [n (%)]	6 (10)	5 (8.3)	0.44
COPD [n (%)]	15 (25)	6 (10)	0.08

**Table 2.** POAF and early complications after operation in both groups

Variables	Control group	Methylprednisolone group	P-value
Incidence of POAF [n (%)]	13 (21.7)	10 (16.7)	0.48
Duration (min)	1287 ± 1202	819 ± 1104	0.34
Recurrence	2.46 ± 1.9	2.1 ± 1.5	0.64
Bleeding [n (%)]	9 (15)	6 (10)	0.40
Infection [n (%)]	5 (8.3)	1 (1.7)	0.20
Vomiting [n (%)]	11 (18.3)	5 (8.3)	0.10
Resp. dysfunction [n (%)]	9 (15)	3 (5)	0.68
Renal dysfunction [n (%)]	9 (15)	4 (6.7)	0.14
Mortality [n (%)]	2 (3.3)	1 (1.7)	1.0
ICU stay (day)	3.01 ± 1.01	2.4 ± 0.8	0.001
Hospital stay (day)	7.48 ± 2.08	5.9 ± 1.2	0.001

POAF occurred in 23 cases (19.2%); from which 10 cases (16.7%) were of MP group and 13 cases (21.7%) from the control group (Table 2). The mean duration of AF was 1084 ± 159 minutes which in the MP group was 819 ± 1104 minutes and in the control group was 1287±1202 minutes ( $P=0.34$ ). Moreover, the frequency of AF recurrence was 2.1 ± 1.5 days in the MP group, 2.46±1.9 days in the control group and 2.3 ± 1.7 days in aggregate ( $P=0.64$ ). This data shows that MP could not decrease incidence, duration and frequency of AF recurrence. Early post-operative complications are compared between two groups in Table 2. ICU stay in MP group was 2.4 ± 0.80 days while this number for the other group was 3.2 ± 1.01 days. Additionally, hospital stay duration was 5.9 ± 1.2 days for the MP group compared to the other group: 7.84 ± 2.08 days. Therefore, MP could significantly reduce ICU and hospital stay. Early mortality after the operation occurred in 3 cases (2.5%) in hospital; one case (1.7%) in the MP group and 2 cases (3.3%) in the control group (Table 2). There was no relationship between administration of MP and post-CABG early mortality.

## Discussion

Our study showed methylprednisolone reduced ICU and hospital stay significantly. However, the incidence, duration and recurrence of POAF and other early complications of surgery did not alter. Atrial Fibrillation (AF) is the most prevalent arrhythmia following CABG surgery and an important cause of morbidity among patients. Its incidence is related to the patient's characteristics and type of surgical operation as well as the procedure and duration of postoperative monitoring (1-3). Recent meta-analysis studies around the effect of

corticosteroids on postoperative patients represent beneficial effects of corticosteroid treatment over placebo; however, its effect is yet controversial (4,5). There were 23 cases (19.2%) of new POAF in this study, whereas in other studies there are reports of 20%-50% of POAF (3-6). In a study conducted by Chaney *et al*, prevalence of post-operative AF in steroid group vs. control group was reported as 26% to 30% (11). In Halverson's study, the incidence of AF was found to be 27.2% in Dexamethasone group, whereas it came up to 32% in control group (9). Whitlock *et al*. injected 250mg MP at the time of induction of anesthesia and CPB (12). MP, however, could not reduce POAF as the same result has been shown in our study. Prasongsukarn injected 43 patients undergoing CABG with 1g MP preoperatively and 4mg Dexamethasone every 6 hours just one day after surgery. He found that AF would considerably subside in corticosteroid group (13). Considering the fact that the subjects in our study were all suffering from severe LV dysfunction and high levels of inflammatory markers and catechol amines in these patients had made them more susceptible to postoperative AF; therefore they were continuously monitored up to 7 days from the time of hospitalization in ICU to that of discharge and postoperative arrhythmias were recorded. In this study, there was no significant relationship between the complications of MP and placebo, however, in Prasongsukaran's study more postoperative complications were reported with MP and dexamethasone group compared with placebo group (13). AF was 17.6% in males whereas it leveled at 22.9% in females indicating no significant relationship between sex and POAF while in other studies male sex has been reported as a predictor of AF (14). The amount of AF incidence in patients within the age group of

lower than 60 years was 10% while this number within the age group of 60 or higher was 25.7% representing a higher incidence of AF when age increases. Increase in age can lead to structural changes such as dilatation of the atrium (15). Mathew *et al.* reported that every 5 years increase in age brings about a higher possibility of POAF around 1.26-1.86 times more thus representing that age can increase the likelihood of POAF (16). The prevalence of POAF in this study was lower compared to that of similar studies due to appropriate care before the operation and good protection of myocardium during the operation. In this study, MP could not decrease the average duration of AF significantly. Also, the 8 mg IV dose of dexamethasone in a study conducted by Halverson *et al.* could not reduce the average duration of AF (9). Our result indicated 5mg/kg of MP could not reduce the frequency of recurrence of AF representing the incapability of MP in reducing the frequency of arrhythmia. In addition, bleeding following CABG surgery was observed in 10% and 15% of patients of the MP and placebo groups respectively which show that low dose of MP could not reduce postoperative hemorrhage. In a study carried out by Whitlock *et al.*, bleeding average turned out to be 505 ml and 609 ml in steroid and placebo groups respectively (12). The results of meta-analysis done by Cappabianca *et al.* suggest that an IV injection of MP can diminish postoperative bleeding (17). In the present study, infection was found in 5% of patients following CABG, 1.7% of which was from the MP group and 8.3% from the placebo group which suggests that MP could not significantly diminish post-CABG infection. By ways of contrast, Cappabianca *et al.* reported that corticosteroids have no effect on postoperative and sternal wound infections (17). Given that corticosteroids reduce migration and activation of inflammatory cells and fibroblasts at the site of sternotomy, they reduce expression of proinflammatory cytokines (18). Steroid-induced immune suppression has been considered to be potentially capable of increasing the risk of postoperative infection. However, in none of the studies corticosteroids increased postoperative infection (17). In our study, the prevalence of postoperative respiratory disturbances had the total number of 10%, 5% for the MP group and 15% for the placebo group representing that MP could not significantly reduce ventilation compared with placebo. Yared *et al.* in their study found that after induction of anesthesia and injection of 0.6 mg/kg of Dexamethasone, the drug facilitates tracheal extubation while a very high dose of MP may hinder early tracheal extubation (19). On the other hand, Cappabianca *et al.*

reported that prophylactic administration of steroids to patients undergoing surgery would not significantly reduce postoperative need to mechanical ventilation compared with placebo (17). In our study, the prevalence of renal disturbances was 10.8%. This in MP and placebo groups turned out to be 6.7% and 15% respectively indicating no significant difference between these groups. Post-CABG vomiting was also observed in 13.3% of patients totally, 8.3% of which from the MP group and 18.3% from the placebo group. Even through corticosteroids have the capability of reducing postoperative vomiting; this dose of MP could not decrease it significantly. Therefore, some doses of corticosteroids can possibly improve absorption of oral medication and thus reduce vomiting. POAF may cause thromboembolism and diminish cardiac output which in turn lead to heightening mortality and longer stay in ICU. In this study, ICU stay lasted  $2.7 \pm 0.96$  days. This number for the placebo group was  $3.2 \pm 1.01$  days but for the MP group was  $2.4 \pm 0.80$  days which represents a significant decrease in the latter group. In terms of the effect of MP on ICU stay, our result is similar to what Whitlock *et al.* found (12). Cappabianca *et al.* reported that prophylactic administration of steroids would significantly decrease ICU stay; however, Halverson *et al.* demonstrated that a low dose of dexamethasone cannot decrease ICU stay (17). POAF need further treatment and longer stay in hospital and can increase hospitalization up to 2-4 days and thus heightening treatment costs. In a study by William Baker *et al.* it was found that corticosteroids would reduce hospital stay approximately 1.6 days compared with placebo (1). Hospital stay in our study turned out to be  $6.6 \pm 1.8$  days,  $7.84 \pm 2.08$  days of which for the control group while  $5.9 \pm 1.2$  days for the MP group which shows a significant decrease. The results of the study by Whitlock *et al.* indicated incapability of MP in decreasing hospital stay which is in contrast with that of our study (12). In this study, 3 patients (1 in the MP and 2 in placebo group) died after the operation indicating that MP could not significantly reduce mortality. Systematic review indicates that prophylactic steroid treatment is likely to reduce postoperative morbidity but is not effective on mortality. These results are similar with our finding (10). We concluded that methylprednisolone reduced ICU and hospital stay significantly. However, the incidence, duration and recurrence of POAF and other early complications of surgery did not alter. Thus we recommend a low dose of MP for patients with severe LV dysfunction who are candidates for cardiac surgery.

## References

1. William L. Baker, C. Michael White, Jeffrey Kluger, Aaron Denowitz, Christopher P. Konecny, Craig I. Coleman. Effect of perioperative corticosteroid use on the incidence of postcardiothoracic surgery atrial fibrillation and length of stay. *Heart Rhythm* 2007;4(4): 461-468
2. Turk T, Vural H, Eris C, Ata Y, Yavuz S. Atrial fibrillation after off-pump coronary artery surgery: a prospective, matched study. *J Int Med Res* 2007;35(1):134-42.
3. Rostagno C. Recent developments in pharmacologic prophylaxis of atrial fibrillation in patients undergoing surgical revascularization. *Cardiovasc Hematol Agents Med Chem* 2009;7(2):137-46.
4. Haghjoo M, Basiri H, Salek M, Sadr-Ameli MA, Kargar F, Raissi K, Omrani G, Tabatabaie MB, Sadeghi HM, Tabaie AS, Baghaie R . Predictors of postoperative atrial fibrillation after coronary artery bypass graft surgery. *Indian Pacing Electrophysiol J.* 2008 Apr 1;8(2):94-101.
5. Kalavrouziotis D, Buth KJ, Vyas T, Ali IS. Preoperative atrial fibrillation decreases event-free survival following cardiac surgery. *Eur J Cardiothorac Surg* 2009;36(2):293-9.
6. Banach M, Kourliouros A, Reinhart KM, Benussi S, Mikhailidis DP, Jahangiri M, Baker WL, Galanti A, Rysz J, Camm JA, White CM, Alfieri O. Postoperative atrial fibrillation - what do we really know?. *Curr Vasc Pharmacol* 2010;8(4):553-72.
7. Dernellis J, Panaretou M. Effects of C-reactive protein and the third and fourth components of complement (C3 and C4) on incidence of atrial fibrillation. *Am J Cardiol* 2006;97(2):245-8.
8. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, Stakos D, Floros D, Papanas N, Chalikias G, Maltezos E, Hatseras DI. Relation of C-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation. *Am J Cardiol* 2006;97(5):659-61
9. Halvorsen P, Raeder J, White PF, Almdahl SM, Nordstrand K, Saatvedt K, Veel T. The effect of dexamethasone on side effects after coronary revascularization procedures. *Anesth Analg* 2003;96(6):1578-83 .
10. 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(3):458-63.
11. Chaney MA, Nikolov MP, Blakeman B, Bakhos M, Slogoff S. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. *Anesth Analg* 1998;87:24-33
12. Whitlock RP, Young E, Noora J, Farrokhyar F, Blackall M, Teoh KH. Pulse low dose steroids attenuate post-cardiopulmonary bypass SIRS; SIRS I. *J Surg Res* 2006;132:188-94.
13. Prasongsukarn K, Abel JG, Jamieson WRE, 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;130:93-8.
14. Liu Y, Liu H, Dong L, Chen J, Guo J. Prevalence of atrial fibrillation in hospitalized patients over 40 years old: ten-year data from the People's Hospital of Peking University. *Acta Cardiol* 2010;65(2):221-4.
15. Siebert J, Anisimowicz L, Lango R, Rogowski J, Pawlaczyk R, Brzezinski M, Beta S, Narkiewicz M. Atrial fibrillation after coronary artery bypass grafting: does the type of procedure influence the early postoperative incidence?. *Eur J Cardiothorac Surg* 2001;19(4):455-9.
16. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA.* 2004 Apr 14;291(14):1720-9.
17. Cappabianca G, Rotunno C, de Luca Tupputi Schinosa L, Ranieri VM, Paparella D. Protective effects of steroids in cardiac surgery: a meta-analysis of randomized double-blind trials. *J Cardiothorac Vasc Anesth* 2011;25(1):156-65.
18. van der Veer WM, Ferreira JA, de Jong EH, Molema G, Niessen FB. Perioperative conditions affect long-term hypertrophic scar formation. *Ann Plast Surg* 2010;65(3):321-5.
19. Yared JP, Starr NJ, Torres FK, Bashour CA, Bourdakos G, Piedmonte M, Michener JA, Davis JA, Rosenberger TE. Effects of single dose, postinduction dexamethasone on recovery after cardiac surgery. *Ann Thorac Surg* 2000;69(5):1420-4.