

Perioperative intravenous corticosteroids reduce incidence of atrial fibrillation following cardiac surgery: a randomized study

Corticosteroides intravenosos no perioperatório reduzem a incidência de fibrilação atrial após cirurgia cardíaca: estudo randomizado

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Abstract

Objective: Corticosteroids decrease side effects after noncardiac elective surgery. A randomized, double blinded, placebo-controlled study was plan to test the hypothesis that standard doses of dexamethasone (6X2) would decrease the incidence of atrial fibrillation (AF) following cardiac surgery.

Methods: A total of 185 patients undergoing coronary revascularization surgery were enrolled in this clinical study. The anesthetic management was standardized in all patients. Dexamethasone (6 mg/ml) or saline (1 ml) was administered after the induction of anesthesia and a second dose of the same study drug was given on the morning after surgery. The incidence of AF was determined by analyzing the first 72 hours of continuously recorded electrocardiogram records after cardiac surgery, to determine the incidence and severity of postoperative side effects.

Results: The incidence of 48 hours postoperative AF was significantly lower in the Dexamethasone group (21/92[37.5%]) than in the placebo group (35/92 [62.5%], adjusted hazard ratio, 2.07; 95% confidence interval, 1.09-3.95 ($P<0.05$). Compared with placebo, patients receiving

dexamethasone did not have higher rates of superficial or deep wound infections, or other major complications.

Conclusions: Prophylactic short-term dexamethasone administration in patients undergoing coronary artery bypasses grafting significantly reduced postoperative atrial fibrillation.

Descriptors: Atrial fibrillation. Cardiac surgical procedures. Dexamethasone.

Resumo

Objetivo: Os efeitos colaterais dos corticosteroides diminuem após a cirurgia eletiva não cardíaca. Este estudo randomizado, duplo cego, placebo-controlado foi planejado para testar a hipótese de que as doses-padrão de dexametasona (6 X 2) diminuiriam a incidência de fibrilação atrial (FA) após cirurgia cardíaca.

Métodos: Um total de 185 pacientes submetidos à cirurgia de revascularização coronária foram incluídos neste estudo clínico. O manuseio anestésico foi padronizado em todos os pacientes. Dexametasona (6 mg/ml) ou salina (1 ml) foram

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Abbreviations, acronyms & symbols	
AF	atrial fibrillation
BMI	body mass index
CABG	coronary artery bypass grafting
CPB	cardiopulmonary bypass
ECG	electrocardiogram
ICU	intensive care unit
SD	standard deviation

administradas após a indução da anestesia e uma segunda dose da mesma droga do estudo foi dada na manhã após a cirurgia. A incidência da FA foi determinada pela análise das primeiras 72 horas de registros de eletrocardiograma continuamente registrados após cirurgia cardíaca, para determinar a incidência e gravidade dos efeitos colaterais pós-operatórios.

INTRODUCTION

Corticosteroids have a variety of beneficial effects on recovery after elective surgery [1-4]. The most common postoperative side effect after coronary artery bypass grafting (CABG) surgery is atrial fibrillation (AF) with a reported incidence of 20%-40% [5-9]. It is associated with increased morbidity, including increased risk of stroke and need for additional treatment, with prolonged hospital stay and increased costs [10-13]. In the previously mentioned study by Yared et al. [6] involving CABG patients at varying risks of developing AF, it was suggested that the administration of dexamethasone (0.6 mg/kg intravenous) reduced the incidence of new onset AF during the first three postoperative days from 32% to 19%.

A recent publication by Fillinger et al. [14] demonstrated beneficial effects of glucocorticoid (methylprednisolone) in suppressing the production of the inflammatory mediators interleukin-6 and interleukin-10 during and after cardiopulmonary bypass (CPB). The pathophysiology of postoperative AF is not fully understood [15]. Cardiac surgery with extracorporeal circulation is known to be associated with a systemic inflammatory response [14], which may be in part responsible for postoperative AF. Complement, C-reactive protein complex levels, and number of white blood cells markers of inflammatory reaction are increased in patients who develop AF [16,17].

A prospective, randomized, double blind, placebo-controlled study was performed to test whether intravenous corticosteroid administration prevents AF after cardiac surgery.

METHODS

The study was approved by the regional ethics committee of Tehran University of Medical Sciences. After

Resultados: A incidência de FA pós-operatória em 48 horas foi significativamente menor no grupo de hidrocortisona (21/92 [37,5%]) do que no grupo placebo (35/92 [62,5%], hazard ratio ajustada, 2,07; intervalo de confiança 95%, 1,09-3,95 ($P < 0,05$). Em comparação com placebo, os pacientes que receberam hidrocortisona não tiveram maiores taxas de infecções da ferida superficial ou profunda, ou outras complicações principais.

Conclusões: A administração da dexametasona profilática de curto prazo em pacientes submetidos à cirurgia de revascularização do miocárdio reduziu significativamente no pós-operatório da FA no pós-operatório.

Descritores: Fibrilação atrial. Procedimentos cirúrgicos cardíacos. Dexametasona.

written, informed consent, 185 patients scheduled for elective CABG surgery were enrolled in this study. We excluded patients with previous episodes of AF or flutter, uncontrolled diabetes mellitus, systemic bacterial or mycotic infection, active tuberculosis, Cushing syndrome, psychotic mental disorder, herpes simplex keratitis or renal insufficiency. We also excluded patients with a history of peptic ulcer or thrombophlebitis.

The patients were randomly allocated to either a control (saline) or dexamethasone (12 mg intravenous). A block randomization scheme was used with 20 patients allocated to each block, to minimize the effects of any subtle changes in therapy during the course of the investigation. To maintain the double-blinded study design, the sealed envelope was opened immediately before surgery, and the study drug was prepared in identical appearing syringes by a nurse who did not participate in the treatment of the study patients.

All patients received standard anesthesia. The first dose of the study medication (either dexamethasone 6 mg intravenous, or saline 1 ml intravenous) was administered after initiating maintenance of anesthesia. All patients underwent median sternotomy and the operations were performed using CBP. All patients were tracheally extubated in the intensive care unit (ICU) when they were judged to be hemodynamically stable with adequate spontaneous ventilator function. On the morning of the first postoperative day, the patients received a second dose of the same study medication (i.e., dexamethasone 6 mg intravenous, or saline 1 ml intravenous).

The occurrence of AF during the postoperative period was assessed by reviewing the continuously recorded electrocardiogram (ECG) data during the first 72 hours after surgery. Episodes of atrial flutter and supraventricular tachycardia were not included in the calculation of the

relative incidences of AF. During the remainder of the hospital stay, the regularity of the patient's heart rate was assessed at 2-hours intervals and ECG monitoring was reinstated if the patient displayed signs of a dysrhythmia.

We defined AF as an episode lasting longer than 5 minutes, regardless of whether it was asymptomatic or required therapy. The number of patients who experienced an episode of AF and the duration of AF were both recorded. The outcomes of this study were the incidences of new onset AF during the first 72 hours after surgery. Proportional data were presented as numbers or percentages in each group, whereas continuous data were presented as means \pm SD. Statistical analysis consisted of a χ^2 contingency analysis or Fisher's exact test for discrete variables and unpaired T test for continuous variables. A value of *P* less than 0.05 was considered significant. A multivariate stepwise regression analysis was performed to identify significant independent predictors.

RESULTS

One hundred eighty five patients were enrolled in this study over a period of 12 months. One was excluded from the efficacy analysis because of development of acute abdominal complications after surgery. The two study groups (n=92 in each) were comparable with respect to their

demographic characteristics and surgical factors (Table 1). In general, the groups were well- matched, although patients randomized to the Dexamethasone group tended to be male. Perioperative characteristics are shown in (Table 1). The mean of central anastomoses (2.9 ± 0.48 vs. 2.6 ± 0.63) significantly differ between the dexamethasone and control groups, respectively (Table 1). Postoperative recovery characteristic of the patient groups is shown in Table 2.

There were 107 patients who had AF during the first 72 hours after cardiac surgery. Patients randomized to the dexamethasone group were significantly less likely to have AF than patients randomized to the placebo group (21/92 [37.5%] vs. 35/92 [62.5%]; adjusted hazard ratio, 2.07; 95% confidence interval, 1.09-3.95, (*P*<0.05) (Table 3). One patient in the dexamethasone group died during the study period as a result of gastrointestinal complications. There were nine postoperative infectious complications, five in dexamethasone group (two pneumonias, and three mediastinal wound infection) and four in the control group (one pneumonias, one urinary tract infection, and two mediastinal wound infection). Four in dexamethasone group and five in the control group developed postoperative myocardial infarction (Table 3). All 184 study patients were discharged from the ICU on the first postoperative day and from the hospital on the fifth or sixth postoperative day.

Table 1. Characteristic of the patient groups

Characteristics	Placebo (n= 92)	Dexamethasone (n= 92)	<i>P</i> Value
Age, mean(SD).y	59.14 \pm 10	60.72 \pm 8.7	0.33
Male sex	63(48.8)	66(51.2)	0.37
BMI	26.52 \pm 2.1	26.77 \pm 2.2	0.44
Surgery time(min)	326.38 \pm 63	327 \pm 58	0.94
Cross- clamp time(min)	42.14 \pm 6.7	43.7 \pm 7.6	0.12
Extracorporeal circulation(min)	72.8 \pm 14.8	74.2 \pm 15.6	0.54
Peripheral anastomoses (n)	3.67 \pm 0.6	3.68 \pm 0.7	0.91
Central anastomoses (n)	2.6 \pm 0.6	2.9 \pm 0.4	0.004*

BMI, body mass index (Kg/m²), Data is mean value \pm SD, numbers (n), and percentages (%). *Significant different

Table 2. Postoperative recovery Characteristic of the Patient Groups

Characteristics	Placebo (n= 92)	Dexamethasone (n= 92)	<i>P</i> Value
Time to tracheal extubation (min)	628 \pm 96	620 \pm 145	0.68
Time to first oral intake(min)	793 \pm 119	707 \pm 283	0.008*
Postoperative bleeding (mL)	421 \pm 160	415 \pm 154	0.76
Able to mobilized [% (n)]			
Postoperative day 1	38.9(14)	61.1(22)	0.54
Postoperative day2	51.7(74)	48.3(69)	0.28

Data are mean value \pm SD, numbers (n), and percentages (%). *Significant different

Table 3. Postoperative side effects of the Patient Groups

Characteristics	Placebo (n= 92)	Dexamethasone (n= 92)	P Value
AF during 24 hours after cardiac surgery[%(n)]	62.5(35)	37.5(21)	0.025*
AF(72 hours after cardiac surgery) [(n)]	62.7(32)	37.3(19)	0.032*
Mortality (n)	1	0	0.31
Myocardial infarction(n)	6	4	0.51
Urinary tract infection(n)	1	0	0.31
Pulmonary infection(n)	1	2	0.56
Wound infection(n)	2	3	0.65

Numbers (n) and percentages (%). *Significant different

DISCUSSION

Atrial fibrillation is the most common arrhythmia occurring after cardiac surgery. Its incidence varies depending on type of surgery. Postoperative AF may cause hemodynamic deterioration, predispose to stroke and increase mortality. Effective treatment for prophylaxis of postoperative AF is vital as it reduces hospitalization and overall morbidity [18]; however, it is believed that the systemic inflammatory response to surgery may play a role in the development of AF [19].

Levels of C-reactive protein are elevated in patients with AF, and prior work has demonstrated that corticosteroids reduce these levels in nonoperative AF [17]. Corticosteroids have anti-inflammatory activity and reduce exaggerated inflammatory reaction [20]. Halonen et al. [19] observed that the concentration of C-reactive protein was significantly lower postoperatively in the hydrocortisone group than in the placebo group. The study by Dernellis & Panaretou [17] also found that corticosteroid therapy reduces both C-reactive protein values and the risk of recurrent and permanent AF in nonoperative patients. We reported the results of the first, to our knowledge, prospective, double-blind, randomized multicenter trial investigating the effects of corticosteroid treatment on the incidence of postoperative AF after cardiac surgery. We found that intravenous dexamethasone reduced the relative risk of postoperative AF by 37.5% compared with placebo in patients undergoing CABG surgery.

The effects of corticosteroid treatment on postoperative AF have been addressed earlier in 2 randomized controlled trials with postoperative AF as the primary endpoint [5,21-22]. Prasongsukarn et al. [21] studied 86 patients scheduled for CABG surgery who were administered 100 mg of methylprednisolone or placebo before surgery and 4 mg of dexamethasone or placebo every 6 hours for 24 hours after surgery. Postoperative incidence of AF was significantly lower (21%) in the corticosteroid group than in the placebo group (51%). Halvorsen et al. [5] administered 4 mg of dexamethasone or placebo after induction of anesthesia and on the first postoperative morning in 300 patients

undergoing CABG surgery. The incidence of postoperative AF was lower among patients randomized to the dexamethasone group vs. the placebo group (27% vs. 32%, respectively). Whereas in our study we administered 6 mg of dexamethasone or placebo after induction of anesthesia and on the first postoperative morning.

In the study by Halonen et al. [19] corticosteroid medication was continued for 72 hours. There was a relatively low incidence of postoperative AF (32%) in the placebo group in the study by Halvorsen et al. [5] compared with the study by Halonen et al. [19] (48%) and our study (37.5%). Methylprednisolone was found to have a statistically significant inhibitory effect on the incidence of AF postoperatively [22]. The study by Yared et al. [6] enrolled 235 patients for CABG. The patients were administered a single dose of 0.6 mg/kg of dexamethasone or placebo after induction of anesthesia.

Compared with the placebo group, the dexamethasone group had a lower incidence of postoperative AF (19% vs. 32%). Although the results of these studies are interesting, it is difficult to compare them with our study. Previous studies have found several predictors of AF after cardiac surgery [23]. To adjust for these confounding factors, we performed a multivariable analysis in which independent predictors such as age, sex; body mass index (BMI), cross-clamp time, surgery time, extracorporeal circulation, peripheral anastomoses, and central anastomoses were taken into account. After adjustment for these factors, corticosteroid treatment remained a significant independent predictor of the absence of postoperative AF. Increased risk of wound infections and gastrointestinal bleeding (stress ulcer) can be a concern with a corticosteroid therapy [20].

We found administration of dexamethasone therapy feasible and well tolerated, and noted no serious complications associated with intravenous administration of the drug. In the study by Prasongsukarn et al. [21], no difference was found between the corticosteroid and placebo groups in major complications, but the corticosteroid groups had minor complications. In our study, there were no more complications in the Dexamethasone group than in the placebo group.

Our study can be criticized because it may have been underpowered to demonstrate significant differences in some of the other secondary outcome measures. This is an important limitation. Another important limitation of our trial is that we included only patients undergoing CABG surgery. The incidence of AF in both study groups (27%-32%) is consistent with the incidence of AF after CABG surgery at most medical centers in the United States [6]. In a recent study, the incidence of AF in the placebo group was 51% [21].

Although hydrocortisone was effective in reducing the incidence of AF, 37.5% of the patients who received corticosteroid treatment had postoperative AF. Further studies have reported that intravenous metoprolol [24], aminodarone [25], bi-atrial pacing [25], and magnesium [26] reduce the incidence of AF after CABG surgery. In conclusion, intravenous administration of corticosteroid therapy is feasible and well tolerated in the prevention of AF after cardiac surgery.

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