THE EFFECT OF ORAL PREDNISOLONE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: *Chronic obstructive pulmonary disease (COPD) is still one of the most important problems in patients undergoing cardiopulmonary bypass (CPB). The purpose of this prospective study was to assess the beneficial effects of oral prednisolone on pulmonary functions in patients undergoing cardiopulmonary bypass.*
Methods: *Forty patients with chronic obstructive pulmonary disease were divided into two groups randomly and were given 20 mg oral prednisolone once daily perioperatively (group I, n= 20) or identical placebo (group II, n= 20). FEV1 values, dates of intensive care unit and hospital stays of the two groups were compared.*
Results: *FEV1 values during the admission to our hospital were similar in each group, mean predicted FEV1: was 56,7± 5,35 % in group I and 57,2± 4,88 % in group II (p= 0,759). After 10 days of oral prednisolone treatment in group I, predicted FEV1 values were significantly different between the two groups (63,2%± 4,24 and %57,9± 4,38) (p= 0,0001). While the predicted FEV1 values revealed a significant difference between two groups at the date of discharge (p= 0,0001) the values became similar at the third month (55,6 %± 4,09 in group I and 55,45 %± 3,87 in group II) (p= 0,897).*
Conclusion: *Various types of complications may occur after cardiopulmonary bypass. Oral prednisolone not only decreases the rates of complications (re-intubation, intubation times, arrhythmia) but also decreases the cost of cardiac operations according to shorter hospital stays.*

Key words: *Oral prednisolone, cardiopulmonary bypass, FEV_1, COPD*

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The effects of oral prednisolone on pulmonary functions in patients were analyzed. Forty patients were divided into two groups and given prednisolone or identical placebo and predicted FEV1 values were measured. Oral prednisolone decreases the rates of complications thus decreases the cost of cardiac operations according to shorter hospital stays.

INTRODUCTION

Coronary Artery Bypass Grafting (CABG) is a safe and effective surgical intervention that is performed successfully with advanced technologic methods and distinctive strategies for a wide range of patients. Recently, CABG has been performed even on elderly patients with co-morbid ities such as chronic obstructive pulmonary disease (COPD) (1). COPD has been considered as a risk factor for early mortality in patients undergoing CABG and forced expiratory volume in one second (FEV1) has been shown to be an independent risk factor for early mortality (2). Vital capacity, functional residual capacity, total lung capacity and pulmonary diffusion capacity are all reduced after open heart operation and return of these variables to their preoperative levels take up to approximately three months (3,4). Postoperative complications such as respiratory failure, re-intubation, sternal dehiscence, prolonged mechanical ventilation, rhythm disturbances and prolonged hospital stays are very common after CABG in COPD patients. Supraventricular tachyarrhythmias (SVT) (commonly atrial fibrillation and multifocal atrial tachycardia) may cause hypotension, congestive heart failure (CHF) or subjective discomfort and anxiety, lengthen the period of postoperative hospitalization, necessitate post hospital medications and increase the total cost of medical care. Systemic embolization during the arrhythmia is another and the most feared complication in COPD patients.

Standard median sternotomy and cardiopulmonary bypass negatively affects pulmonary functions in patients without any pulmonary problems previously. Pleurotomy during harvesting of left internal mammary artery (LIMA), pain (due to chest tubes and incisions) also negatively influences the patients' ventilation capacity (5).

In this prospective study, we attempted to answer if the prophylactic oral prednisolone therapy is necessary or not on pulmonary functions in COPD patients undergoing CPB.

MATERIAL AND METHOD

Study Design:

After Local Research Ethics Committee approval and informed consent were obtained, 40 patients with chronic obstructive pulmonary disease undergoing coronary artery bypass grafting were enrolled in the study.

This prospective study was done between January 2000 and January 2003. The aim of our study was to investigate the effect of prophylactic oral prednisolone administration for reducing both pulmonary and non-pulmonary complications and increasing the FEV1 values in patients with COPD undergoing coronary artery bypass surgery. We included the patients with COPD who had positive physical examination findings (sputum, cough, wheezing, paradoxical inspiratory indrawing of the lateral rib margin known as Hoover's sign), predicted FEV1 value less than 70% and FEV1/ FVC less than 70 %. The symptoms of the patients were shown in Table I.

Table I: Preoperative patients' characteristics and operative variables.

	Group I (n: 20)	Group II (n: 20)	P value
Male/Female	16/4	15/5	0,5
Age	63,7±6,22	63,8± 6,67	0,961
Previous MI	13	14	0,5
Hypertension	7	9	0,374
Preoperative Stroke	1	2	0,5
Hx of smoking	18	17	0,672
Cough	20	20	1,00
Sputum	14	12	0,482
Wheezing	9	7	0,374
Hoover's sign	5	6	0,5
Mean predicted FEV1(%)*	56,7± 5,35	57,2± 4,86	0,759
LVEF (%)	55,05± 3,79	55,95± 4,86	0,446

***FEV1 = Forced Expiratory Vital Capacity in first second (on admission)**
COPD = Chronic Obstructive Pulmonary Disease
MI= Myocardial Infarction

The patients who have a familial history of atopy, uncontrolled left ventricular failure, clin-

ical or radiological evidence of pneumonia, arterial blood ph < 7.30, ejection fraction (EF) less than 35%, history of COPD treatment and concomitant valvular operations and insulin dependent diabetes mellitus were excluded from our study. All re-operative and off-pump procedures were excluded from the study. During the period of our study, the number of the COPD patients who underwent coronary artery bypass surgery was 40. These patients were divided into two groups randomly by using random numbers on the computer. Each group included 20 patients. Our study team, the patients and the spirometry technician were blind to the study whereas the pharmacist and the statistical data analysts were not blind to the coding of the groups. On admission to our hospital; spirometry was done to each patient after bronchodilator nebulisation. We decided to give 20 mg oral prednisolone daily to the group I patients (n: 20) and placebo to the other patients (group II, n: 20). In group I, oral prednisolone (20 mg/daily) was given to the patients beginning 10 days before the operation and continued to the date of discharge. During the postoperative period, the dosage of oral prednisolone was reduced to the half of initial dose at every third day, whereas placebo was given to the other group patients. After the withdrawal of prednisolone (at the time of discharge), spirometry was done to all patients and FEV1 values were compared. FEV1 values were compared at the postoperative 3rd month again. Patients' characteristics in the preoperative period and performed operations are summarized in Table-I. Extubation times, date of intensive care unit, hospital stays, pulmonary and non-pulmonary complications, and additional surgical and non-surgical interventions were compared.

Operative Characteristics: In all patients a LIMA graft was used. All patients were operated on by using median sternotomy and cardiopulmonary bypass technique. Cardiopulmonary bypass (CPB) was established in all patients with single venous and aortic cannula. Membrane oxygenator (Capiox-E Terumo Corp, Tokyo, Japan) was used in all cases. Moderate hypothermia to 28°C and topical cooling with iced saline slush were used in all patients. Myocardial preservation was accomplished with the use of intermittent antegrade St. Thomas II solution and topical ice slush. Phrenic nerve pad was used in all cases in order to prevent any phrenic nerve injury. Cardiopulmonary bypass (CPB) was established with a roller pump and non-pulsatile flow after anticoagulation with bovine lung heparin (3 mg/kg) and activated clotting time was maintained for more than 480 seconds. Heparin was reversed by protamine (3.5 mg/kg) at the end of the cardiopulmonary bypass. All distal anastomoses were done in a single cross clamp period.

After the operation, the patients were transferred to the intensive care unit. Ventilation was in a volume-controlled mode (Dräger Evita Dura 2, Germany) with a tidal volume of 10 ml/kg and 10-15 breaths/ min. The patients were extubated according to the hemodynamic states and blood gases samples.

Sampling sizes:

We predicted a 10% increase of predicted FEV1 values with oral prednisolone prophylaxis. To detect this difference with 95% confidence limits and power of 90%, we needed to enter at least 13 patients into each groups (6)

Statistical Analyses:

Statistical analysis was performed with SPSS software version 10.0 (SPSS Inc, Chicago, III). Clinical data were expressed as mean values ± standard deviation. Differences were analyzed with Levene's test, Mann- Whitney U test and Chi-Square test. The effects of the variables were investigated by using the Univariate and multivariate logistic regression analyses.

RESULTS

Following bronchodilatation the wet spirometry (Sensormedics 2400, Holland) revealed no significant difference between two groups (mean predicted FEV1: 56,7± 5,35 % in group I and 57,2± 4,88 % in group II (p= 0,759) and

in all patients the value was FEV1/ FVC < 70%. In group I the patients were treated with 20 mg prednisone for 10 days and then spirometry was repeated to all patients. After 10 days of therapy in group I, greater improvements were observed in FEV1 (63,2± 4,24 %) than group II (57,9± 4,38 %) (p= 0,0001). On the operation day 20 mg oral prednisone was given to the group I patients and placebo to the group II. Operative characteristics revealed no significant differences between two groups. Average cross-clamp and CPB times were summarized in Table II.

Table II: Postoperative variables of two groups.

	Group I	Group II	P value
Cross-Clamp Time	(min)	46± 4,65	4 7 , 2 ±
4,28	0,402		
CPB Time	(min)	66,8± 5,81	6 8 , 9 ±
5,67	0,956		
CABG+Carotid			
Endarterectomy	-	1	0,5
CABG+Bullectomy	1	1	0,756
Average Graft No.	2,6±0,99	2,7±0,95	0,744
LIMA	20	20	1
Radial Artery	6	5	0,5
Bronchospasm	1	3	0,302
Tracheostomy	-	1	0,5
Re-intubation*	-	6	0,01
Sternal Dehiscence	-	1	0,5
Wound Infection	-	2	0,244
Arrhythmia	1	4	0,171
ICU Stay (day)	1,4± 0,68	5,2± 3,25	0,0001
Hospital Stay (day)	8,3± 1,17	12,95± 2,95	0,0001
Hospital Mortality	-	2	0,244
Pleural effusion**	1	4*	0,171

CPB=Cardiopulmonary Bypass
ICU= Intensive Care Unit
MI=Myocardial Infarction
CABG= Coronary Artery Bypass Grafting
LIMA= Left Internal Mammary Artery
* Re-intubation periods included
* Two times in one patient

Contrary to group I, mean extubation time, dates of intensive care unit and discharge, re-intubation rates, pulmonary and non-pulmonary complications were higher in group II (Table 2). Three patients in group II were re-intubated according to the blood gases analyses and hemodynamic criteria. Tracheostomy was required in 1 patient among the re-intubated patients. Sternal dehiscence was observed in one patient in group II and external chest support (Heart Hugger-Sternum Support Harness) was used. Superficial wound infection on the sternotomy incision occurred in 2 patients in group II. Atrial fibrillation was observed in four patients (1 patient in group I and 3 patients in group II). Ventricular fibrillation occurred in one patient in group II (the patient died). Two patients in group II (in whom tracheostomy was done in one case and ventricular fibrillation in the other) died during the early postoperative period. At the date of discharge spirometry was repeated to all patients. Oral prednisolone was withdrawn at the postoperative 7th day, by decreasing the half of initial dosage at each 3 days. According to the median sternotomy, pleurotomy and incisional pain mean predicted FEV1 values decreased in both groups whereas the decrease was significant in group II (47,05± 3,22 % versus 55,15± 2,98 %) (p= 0,0001). Spirometry was repeated in the third postoperative month and observed that FEV1 values were similar to the preoperative values (55,6± 4,09 % in group I and 55,45± 3,87 % in group II) (p= 0,897). During the follow-up period, pleural effusion was observed in only one patient in group I whereas, it was observed in three patients in group II (twice in one patient).

Table III: Perioperative differences of predicted FEV1 values.

Predicted FEV1 values(%)	Group I	Group II	P value
On admission	56,7± 5,35	57,2± 4,86	0,759
Before operation	63,2± 4,24	57,9± 4,38	0,0001
Before discharge	55,15± 2,98	47,05± 3,22	0,0001
3rd month	55,6± 4,09	55,45± 3,87	0,897

CONCLUSION

COPD is one of the most leading causes of chronic morbidity and mortality in the world (7,8). In COPD, lung parenchyma, airways and pulmonary vasculature are affected. Recent studies strongly proved the development of lung injury after Cardiopulmonary Bypass

(CPB), even in the preoperatively completely normal functioning lung (9,10). Lung injury becomes more prominent after surgery in COPD patients. Pulmonary variables returned to their preoperative levels in approximately 4 months in COPD patients (3,4). Several studies have been made to establish COPD as a risk factor for mortality in patients undergoing CABG (1,11,12). The Society of Thoracic surgeons established COPD as an operative risk factor and Cleveland Clinic score has allotted COPD a value of 1 (12). The Veterans Administration showed that patients undergoing CABG with an FEV1 less than 1.25 L have a significantly higher acute mortality rate (2). Detailed quantitative analysis of the influence of COPD on patients undergoing CABG has not been done.

After cardiac surgery pneumonitis, atelectasis and bronchospasm are the mostly observed complications (% 40) (13). Pulmonary complications following the cardiac surgery are affected from two main factors: 1) Extra-CPB factors such as general anesthesia, median sternotomy, pleurotomy, pain, chest tubes. Median sternotomy and pleurotomy during LIMA graft harvesting decreases the spirometric values (14,15). Shapira et al reported that median sternotomy had significantly reduced the peak expiratory low rate and lung volumes after cardiac surgery (16). Surgical pain, tenderness and chest tubes also decrease the lung volumes. 2) Intra-CPB factors are heparin-protamine reactions, hypothermia, and cardiopulmonary arrest (11). These problems provoked the investigators to research new techniques and methods. Güler et al compared the three different operative techniques in patients with COPD. They reported that off-pump bypass technique and minimally invasive direct coronary bypass grafting technique had superiority on pulmonary functions when compared with median sternotomy (17).

Oral glucocorticoids are still one of the most important therapies for the treatment of COPD. Some authors claimed that a dose of >7.5 mg.day-1 was sufficient for the treatment of COPD (18). They suggested that their theories were based on the increasement of FEV1 values after the therapy of glucocorticosteroids. Albert et al reported that most of the patients receiving methylprednisolone exhibited increases in FEV1 greater than 40% (19). Moreover, Davies and Niewoehner reported good results of methylprednisolone and prednisolone during the treatment of COPD (20, 21). However; some authors suggested no improvements in lung volumes. Emerman and co-workers reported that no improvement was observed in spirometric parameters with a single dose of methylprednisolone (22). Furthermore Rostom and Wood-Baker also observed poor improvements in FEV1 values (23, 24). In our prospective study we observed significant improvement in FEV1 values after 10 days of treatment with oral prednisolone between the two groups.

The association of COPD with an increased incidence of ventricular and supraventricular arrhythmias is well established. Especially supraventricular arrhythmias are common after CABG in patients with COPD patients (25, 26). Hospitalized patients with COPD have as high an incidence of arrhythmias as 89%. Poor ventilatory mechanics and atelectasis of the lung in the postoperative period will aggravate ventilation perfusion (V/Q) mismatch and hypoxia. Atrial fibrillation decreases the cardiac output and leads to further deterioration of hypoxemia that can be fatal if not corrected. COPD patients have frequent premature atrial contractions that predisposes them to atrial fibrillation (27, 28). The COPD proved to be a predictor of AF. Leitch et al. found a similar association between COPD and AF in their retrospective review of 5807 patients who underwent CABG in an earlier era. Our study also confirmed the all above-mentioned studies (29). In our study, rhythm disturbances were observed; in only one patient in group I; whereas in 4 patients in group II and the patient in whom ventricular fibrillation was observed in group II died at the third postoperative day.

COPD is still one of the major problems after cardiac surgery. COPD also provokes other complications (cardiac and non-cardiac) during the early postoperative period. It's proved that most of pulmonary changes stimulated by CPB

recovered in the post operative three or five months. Blood gases level and chest mechanics return to their preoperative level at the postoperative 3 or 5 months (3, 4). In our study, the predicted FEV1 values became similar in both groups at the postoperative third month controls.

Conclusion: Preoperative short-term oral prednisolone therapy significantly improves the patients' lung volumes. Preoperative improvement also continues during the early postoperative period, during which the most complications occurred. As a result we suggested that preoperative oral prednisolone strongly increases predicted FEV1 values whereas strongly reduces cardiac and non-cardiac complications, extubation times, ICU and hospital stays, therefore reduces hospital costs.

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