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ARAŞTIRMA YAZISI / *ORIGINAL ARTICLE*

The Effect of Preoperative Smoking on Postoperative Cerebrovascular Accidents in Diabetic Patients Undergoing to Coronary Artery Bypass Graft Surgery

Koroner Arter Bypass Grefti Cerrahisine Giden Diyabetik Hastalarda Preoperatif Sigara Kullanılmasının Postoperatif Serebrovasküler Olaylar Üzerine Etkisi

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ABSTRACT

AIM: *The study was designed to investigate the correlation between preoperative cigarette smoking and postoperative cerebrovascular accidents (CVA) after coronary artery bypass graft (CABG) surgery in diabetic patients.*

METHODS: *This prospective observational study included 135 diabetic patients underwent coronary artery bypass graft surgery between January 2008 and August 2011. The participating patients were divided into two groups as: Group 1 (n=17) smokers and Group 2 (n=118) non-smokers. Preoperative risk analysis for estimating the post operative CVA was performed by using the criteria of American Heart Association (ACC/AHA) updated in 2004. According to the criteria, assumed postoperative CVA risks ranged between 0.6% and 2% (mean rate for all patients was 1.04±0.4%). Until the postoperative 60th day, all patients were integrated in a follow up programme to scan and diagnose a probable CVA. Patients with symptoms, signs and suspicions of CVA were evaluated by a series cranial tomography scanning and a multi-disciplinary approach in conjunction with the departments of radiology and neurology. Statistical analysis was performed using Student's t test, Fischer's exact test, Yates' correction chi-square test and Mann-Whitney U test. A p value <0.05 was considered statistically significant.*

RESULTS: *There were 83 male and 52 female participants. The number of males was significantly higher than the females in both the smokers (88.2%) and the non-smokers groups (57.6%), (p<0.05). The rate of the male patients in the smokers group was also significantly higher than the rate of the smokers in the non-smokers group (p<0.05). The rate of patients with insulin dependent DM was 52.9% and 30.5% in the smokers and non-smokers group, respectively, however the inter group difference was not significant (p>0.05). The rate of preoperatively defined estimated postoperative CVA risk, intra-operative pump use and cross-clamping durations did not show significant differences between the smokers and non-smokers (p>0.05). There were two postoperative CVA (11.8%) cases in the smokers and two CVA cases in the non-smokers (1.7%) groups. The rate of CVA was significantly higher among the smokers in comparison with the non-smokers (p<0.05).*

CONCLUSION: *Smoking in the last six months before attending to the department of cardiovascular surgery for isolated CABG surgery increases the risk for post operative CVA in diabetic patients.*

Key words: *cigarette smoking; coronary arteries; coronary artery bypass grafting; cerebrovascular accident; diabetes mellitus*

ÖZET

AMAÇ: *Bu çalışma koroner arter bypass cerrahisi (KABC) uygulanan diyabetik hastalarda gelişebilecek postoperatif serebrovasküler olay (SVO) ile preoperatif sigara içiminin ilişkisini araştırmak için düzenlenmiştir.*

YÖNTEM: *Bu prospektif çalışmada Ocak 2008 ve Temmuz 2011 tarihleri arasında KABC geçiren 135 hasta yer aldı. Hastalar iki gruba ayrıldılar. Grup 1 sigara içenler (n=17), Grup 2 ise sigara içmeyenlerden oluşuyordu (n=118). Postoperatif öngörülen SVO riski için Amerikan Kalp Derneği'nin 2004'de güncellediği ölçüt kullanıldı. Kriterlere göre tahmini postoperatif SVO riski %0,6 ile %2 (bütün hastalar için ortalama %1,04±0,4) arasında değişti. Bütün hastalar postoperatif olası SVO'yu tanıyabilmek için ameliyat sonrası 60 günlük takip programına alındılar. SVO açısından belirti, bulgu ya da şüphesi olan hastalar; radyoloji ve nöroloji bölümleri ile işbirliği altında multi-disipliner yaklaşım ve seri kraniyal tomografilerle değerlendirildiler. İstatistiksel analiz Student t, Fischer'in kesinlik, Yates'in düzeltmeli ki-kare testi ve Mann Whitney U testleri kullanılarak yapıldı. P değerinin 0,05'ten küçük olması anlamlı sayıldı.*

BULGULAR: *Katılımcıların 83'ü erkek ve 52'si kadındı. Hem sigara içenlerin (%88,2) hem de içmeyenlerin (%57,6) grubunda erkekler kadınlara göre anlamlı derecede daha fazlaydılar (p<0,05). Sigara içenler grubundaki erkek oranı, sigara içmeyenler grubundaki erkek oranından da anlamlı derecede fazlaydı (p<0,05). İnsüline bağımlı DM oranı sigara içenler grubunda %52,9 ve içmeyenler grubunda %30,5'ti, ancak iki grup arası fark istatistiksel olarak anlamalı değildi (p>0,05).*

Preoperatif olarak belirlenen tahmini postoperatif SVO oranı, intraoperatif pompa ve çapraz klampleme zamanları açısından gruplar arası anlamlı farklılık saptanmadı (p>0,05). Sigara içenler grubunda iki (%11,8) ve içmeyenler grubunda iki (%1,7) postoperatif SVO görüldü. Postoperatif SVO oranı sigara içenlerde anlamlı derecede yüksekti (p<0,05).

SONUÇ: *KABC için kardiyovasküler cerrahi bölümüne başvurudan önceki son altı ayda sigara içmek, diyabetik hastalarda postoperatif SVO riskini arttırır.*

Anahtar kelimeler: *sigara içmek; koroner arter bypass graftlemesi; serebrovasküler olay; diyabetes mellitus*

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Introduction

Coronary artery disease (CAD) is a significant health challenge encountered across the world. World Health Organization (WHO) calculated in 2008 that China, Russia and India would spend grossly $200–250 billion for heart diseases, stroke and diabetes mellitus (DM) during next decade[1].

Coronary artery bypass grafting (CABG) is a surgery reserved for patients with CAD and includes the risk of cerebrovascular accidents (CVA). CVA secondary to CABG has two subgroups as type 1 includes focal cerebral infarct and transient ischemic attacks, and type 2 is characterized by intellectual disruption and disorientation. Both subtypes are important as they may be fatal.

Diabetes Mellitus is a well-established and independent leading risk factor for stroke. It causes serious pathological changes in the cerebral vessels[2] and these changes play role in the mechanism of CVA. Smoking, inhalation of the smoke of cigarettes and other tobacco products, also increases the risk for stroke[3].

In this study we aimed to investigate the relation between smoking and postoperative CVA in diabetic patients who had an isolated on-pump CABG surgery.

Materials and Methods

This prospective observational study included 135 coronary artery bypass graft surgery patients operated between January 2008 and August 2011 in the Department of Cardiovascular Surgery. Before the initiation of the study, the local ethics committee approved the study.

The candidates of CABG surgery (n=135) diagnosed with CAD and DM were involved in the study. The participating patients were divided into two groups as: Group 1 (n=17) cigarette smokers and Group 2 (n=118) non-smokers. Group 1 patients were actual smokers who smoked until they attended to our department, however Group 2 patients were either non- smokers or those gave up smoking at least six months before they attended. None of the patients smoked after they attended to our cardiovascular department.

The patients, in whom the CABG was not an option were excluded. Giving up smoking in the last 6 months also caused exclusion. The chronic diseases and life threatening conditions also caused exclusions. Those included the coexisting chronic obstructive pulmonary disease (COPD), being in a dialysis program, a serum creatinine level higher than 2mg/dl, a stenosis of more than 75% of the carotid arteries, a macroscopic plaque in the aorta diagnosed during the surgery and a history of CVA. Patients undertaken to emergent or urgent surgeries or died from a reason other than CVA were also excluded.

Preoperative risk analysis for estimating the post operative CVA was performed by using the criteria of American Heart Association (ACC/AHA) updated in 2004. According to the criteria, assumed postoperative CVA risks ranged between 0.6% and 2% (mean rate for all patients was 1.04±0.4%). The CVA risk scores in association with other risk factors were used for assessing the optimal time for the surgery as emergent, urgent or planned. Other risk factors used in the assessing process included the age, sex, DM, COPD, carotid artery disease, need for dialysis, serum creatinine levels over 2mg/dl and an ejection fraction (EF) below 40%.

All patients were questioned for their previous medical and smoking status. We carried out a detailed physical examination for each participant. The standard preoperative laboratory work up included but not limited to a respiratory function test, a trans-thoracic echocardiography, and a bilateral carotid artery Doppler study.

Probable calcifications in the ascendant aorta and the aortic arch was evaluated preoperatively using a standard telegram. The ascendant aorta and the initial segment of the aortic arch were also prone to an intra-operative meticulous manual examination. In order to prevent cannulation during palpation, altered operative procedures were used in patients with plaques, and the alteration of the approach led to the exclusion of the patients with plaques.

We performed all CABG surgeries with the support of the bypass of the cardiopulmonary circulation, and used side clamps for proximal anastomosis.

Along with enteral feeding, 100 mg/day aspirin was given postoperatively to all patients to decrease the risk of stroke. A rigid schedule was used to regulate the blood glucose levels both in preoperative and postoperative periods. A combination of insulin glargine 100 IU/ml (Lantus® flacon, Sanofi Aventis) and human soluble regular insulin 100 IU/ml (Humulin-R® flacon, Lilly) was used in appropriate

and individualized doses for each patient. Insulin infusion was used on demand and blood glucose levels of all patients were maintained under 200 mg/dl.

Until the postoperative 60th day, all patients were integrated in a follow up programme to scan and diagnose a probable CVA. Patients with symptoms, signs and suspicions of CVA were evaluated by a series cranial tomography scanning and a multi-disciplinary approach in conjunction with the departments of radiology and neurology.

Statistical Analysis

All statistical data were analyzed with a SPSS package program (SPSS Inc., Chicago, IL, USA). Continuous variables were presented with minimum, maximum and mean±standard deviation values, and categorical variables were presented with frequency and percentage values. Student's *t* test was used to indicate independent variables. Fisher's exact test was used to evaluate the anticipated variables observed less than 5 times, and Yates' correction chi-square test was used to compare categorized variables. Mann Whitney U test was used to compare rates of CVA. A p value <0.05 was considered statistically significant.

Results

There were 83 male and 52 female participants. The demographic data consisting of the age and gender and the data dealing with the diabetes type, ejection fraction and the rate of CVA were summarised in Table 1. The number of males was significantly higher than the females in both the smokers (88.2%) and the non-smokers groups (57.6%), ($p<0.05$). The rate of the male patients in the smokers group was also significantly higher than the rate of the smokers in the non-smokers group ($p<0.05$).

The ages of the participants were not significantly different in both smokers and non-smokers groups ($p>0.05$). The rate of patients with insulin dependent DM was 52.9% and 30.5% in the smokers and non-smokers group, respectively, however the inter group difference was not significant ($p>0.05$). The comparison of percentages of patients with ejection fractions lower than 40% did not show significant differences between the smokers and non-smokers ($p>0.05$).

The rate of preoperatively defined estimated postoperative CVA risk (Table 1), intra-operative pump use and cross-clamping durations (Table 2) did not show significant differences between the smokers and non-smokers ($p>0.05$).

Table 1. *The comparison of the diabetic patients underwent to coronary artery by-pass surgery according to their smoking status. The data is presented as mean ± SD, median or percentage values, appropriately.*

Parameter	Smokers (n=17)	Non-smokers (n=118)	p value
Age of the patients	58±10	61±8	0,06
Male gender (%)	15 (88%)	68 (58%)	0,015**
Insulin dependent DM (%)	9 (53%)	36 (31%)	0,118**
Patients with EF < 40% (%)	4 (24%)	19 (16%)	1*
Preoperative risk of CVA***	0.88±0.3	1.06±0.41	0,08
Postoperative CVA (%)	2 (12%)	2 (2%)	0,023†

*An expected cell value is less than 5. Fischer exact result was given.
**Chi-Squares with Yates corrected result was given.
***Percentage of risk for estimated post operative cerebrovascular accidents calculated preoperatively.
†Mann Whitney U result was given.

Table 2. *The comparison of the diabetic patients underwent to coronary artery by-pass surgery according to their smoking status. The data is presented as mean±SD.*

Parameter	Smokers (n=17)	Non-smokers (n=118)	p value
Cardiopulmonary bypass time(minute)	105±22	105±30	0,97
Cross clamp use time(minute)	74±20	71±22	0,64

Table 3. *The summary of characteristics of the four cerebrovascular accident (CVA) patients*

Case no	Gender	Age	Ejection fraction	Preoperative CVA risk (%)	Smoking
1	female	43	< 40%	1,4%	+
2	male	63	≥ 40%	0,9%	+
3	male	75	≥ 40%	1,3%	-
4	female	66	< 40%	2%	-

During the course of the study, we observed four cases of CVA. The clinical manifestations were as an ischemic optic neuritis, a transient ischemic attack, a left hemiplegia and a massive ischemic encephalopathy. There were two CVA (11.8%) cases in the smokers and two CVA cases in the non-smokers (1.7%) groups (Table 3). The rate of CVA was significantly higher in the smokers in comparison with the non-smokers ($p<0.05$).

Discussion and Conclusion

In a population-based survey (TURDEP), the prevalence of smoking was 51% in men and 11% in women in Turkey[4]. Both passive and active smoking increases the concentrations of carboxyhaemoglobin and the fibrinogen, and enhances the aggregation of the platelets. Smoking also decreases the concentrations of the high density lipoprotein cholesterol. Animal studies showed that smoking accelerates the atherosclerotic process due to a direct toxic effect with 1, 3-butadien, and thus elevates the risks for heart disease and stroke[5].

Free oxygen radicals, also called as reactive oxygen species (ROS), or reactive anions cause oxidative stress in cellular levels. These reaction-forming structures may interact with other molecules involving oxygen atoms and trigger the production of other free radicals. An increase in oxidant levels, a decrease in antioxidant levels and the failure in the management of oxidative stress result in the accumulation of ROS[6-9]. In a healthy person, to clear ROS, some enzymes like superoxide dismutase, catalase, and glutathione peroxidase work in the intra cellular environment and some antioxidant vitamins, such as vitamins C and E work in the extra cellular environment. Cigarette smoke contains huge amounts of superoxide and other reactive oxygen types such as hydroxyl radical, hydrogen peroxide and peroxynitrite. Degenerative effects of smoking arise when the free radicals in smoke oxidise macromolecules. In vivo and in vitro studies indicated that externally administered antioxidants were partially protective against the inflammation and oxidative stress resulted by smoking[10-11]. This finding strongly supports the hypothesis that most of the harmful effects of smoking are the results of the oxidative stress caused by ROS[12-15].

Smoking leads to a pre-atherosclerotic condition by forming a pro-inflammatory response in leucocytes via cytokine signals, causes an increase in matrix metalloproteinase concentrations, and enhances the adhesion and the attachment of the monocytes to the endothelium of the blood vessels[16,17]. Elevations in the leukocyte counts, particularly the neutrophil and monocyte counts, are common among smokers[18]. Free radicals released from neutrophiles are believed to have a damaging effect on vessel endothelial cells[19].

Cigarette smokers are also at high risk in terms of thrombosis. It was demonstrated in in-vivo and in-vitro studies that smoking increased the levels of the platelet factor, Von Willebrand's factor, catecholamine and thromboxane and resulted in more active platelets in smokers[20,21]. C reactive proteins led to endothelial dysfunction by decreasing nitric oxide production and endothelial bioactivity[22].

There have been a quite a lot studies searching for the correlation of smoking and the stroke. The researchers of many studies conducted within various populations and ethnic groups, concluded that smoking had a strong correlation with stroke. They also argued that the risk for stroke was twice to four times higher among smokers, in comparison to lifetime non-smokers and those who had given up smoking for the last ten years or more[3,23,24]. In a study, the risk for stroke was six times higher in cigarette smokers, compared to lifetime non-smokers and non-second hand smokers[25]. In another study, smoking was associated with a risk increase of nearly 50% for stroke and cerebral infarcts[26]. The increased risk is considered to arise from procoagulant and atherogenic effects of smoking[27].

Giving up smoking following CABG surgery was found to improve some health measures crucially, such as decreases in the recurrent angina pectoris and hospital application rates, and increases in the functional capacity and the total survival rates[28]. In contrary, the patients insisting on smoking after CABG surgery were markedly at a higher risk for myocardial infarction and reoperation[29]. In our study, continuation of smoking until the admission to hospital increased the post operative CVA rates ($p=0.023$).

DM is another independent risk factor for stroke. DM causes vascular disorders. These disorders are observed as clinical diseases such as coronary artery disease, stroke, left ventricular hypertrophy, atrial fibrillation and peripheral artery disease[30].

Limitations of the Study

The duration and the amount of smoking could not be documented in the smokers group and in the patients who gave up smoking. Some of the data were missing and some patients were unable to remember the exact duration and amounts. Therefore we preferred to use the preoperative CVA risk scoring scale.

The duration, type and the severity of the diabetes mellitus and its contribution to the CAD was not clear. The long term and peri-operative regulation of and the control of blood glucose levels were not well established. The type of medication, insulin or oral anti diabetics, was not definitively defined as insulin was the preferred peri-operative treatment option.

The second hand smoke exposure was not clear. The hazards of smoking were only based on individual smoking and its direct exposure.

In some patients, the duration and amount of smoking, insulin use and the duration of the DM and CAD were not recorded and those missing records prevented the analysis of those characteristic. Therefore, future prospective controlled studies using larger samples are needed.

Although the methodology of the study prevents high level evidences, we may conclude that smoking in the last six months of attending to the department of cardiovascular surgery for isolated CABG surgery increases the risk for post operative CVA in diabetic patients.

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Declaration of Interest

None declared

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