SCIENCE AND TECHNOLOGY - Research Journal - Volume 3 - 1999
University of Mauritius, Réduit, Mauritius.

IS FIBRINOGEN A RELIABLE HAEMOSTATIC MARKER FOR MONITORING POSSIBLE RISKS OF THROMBOEMBOLIC EVENTS IN SMOKERS?

by

A. H. SUBRATTY* *and* M. BEERBUL

Department of Health & Medical Sciences, Faculty of Science,

University of Mauritius, Réduit, Mauritius

(Received September 1998 –Accepted October 1998)

ABSTRACT

With the increasing incidence of smoking in Mauritius, the present work was designed to investigate the potential effects of smoking on blood coagulation parameters. The present study is based on data collected from 118 male participants that consisted of 100 smokers and 18 non-smokers. Blood coagulation parameters included measurements of fibrinogen level, activity of cofactor VIII and prothrombic activity by using commercially available colorimetric kits. Analysis of variance showed that fibrinogen levels in smokers were significantly higher than in the non-smokers ($P<0.05$). However there were no statistically significant differences for the other haematological parameters measured for both the control and smokers ($P>0.05$). We thus concluded that fibrinogen could be a reliable marker for monitoring risks of thromboembolic events in smokers.

Keywords : Haematology, smoking, fibrinogen, thromboembolic events.

INTRODUCTION

Cigarette smoking is a serious health problem to smokers and to those exposed to it. Lung cancer is the major danger for smokers but diseases of the blood vessels and the heart account for over one third of all excess death in smokers (Leone, 1993).

**For correspondence and reprints*

Cigarette smoking has been reported to be a risk factor for coronary arterial disease that usually has no single cause. Factors implicated in the aetiology of the disease include genetic predisposition, obesity, high blood pressure, elevated serum lipids (particularly total cholesterol and low density lipoprotein), smoking, diabetes and lack of physical activity (Cotellaro & Boschetti, 1992). A combination of these risk factors is usually responsible for thromboembolic accidents in high-risk patients.

In most cases the immediate cause of myocardial infarction (heart attack) is the formation of an occlusive thrombosis in the coronary arteries. From various reports it can be seen that cigarette has several adverse effects on coagulation mechanism that ultimately lead to thrombosis. Adverse effects such as atherosclerosis, cell damage, impaired endothelial vasodilatation, activation of platelets and increase in Von Willebrand factor have been associated with smoking (Penn & Caroll, 1991). One of the most common adverse effects of smoking is atherosclerosis. This refers to the focal thickening of the arterial wall so that the artery becomes partially or completely occluded. This phenomenon has been reported to be the mechanism mainly responsible for cardiovascular diseases in smokers (Cawley, 1983).

Smoking is also associated with peripheral vascular damage and has been shown to increase platelet aggregation in response to ADP. Experiments have shown that smoking has disruptive effects on the vascular endothelium, leading to appearance of bleb-like protrusion on the luminal surface. In addition, tobacco smoke has been shown to be mitogenic for arterial smooth muscle cells (Cawley,1983).

The presence of atherosclerosis in the coronary arteries is a *sine qua non* for the development of coronary thrombosis and myocardial infarction in the majority of cases, (Jan Hakkan, 1991). This is most likely to happen at areas of increased turbulence, such as branching points of arteries within the high-pressure coronary circulation. In these high sheer conditions, Von Willebrand factor attaches to platelet surface glycoprotein receptor and may bind other proteins such as collagen and fibronectin.

Platelets, which are in contact with damaged or disrupted endothelium become activated and release the contents of granules, including platelet-derived growth factor (PDGF), fibronectin, Von Willebrand factor and fibrinogen. These factors stimulate the proliferation of smooth muscle cells in the intima of arterial blood vessels and promote the migration of fibroblast from the media to the intima of the vessel wall.

Several reports suggest a relationship between increased platelet activity and thrombogenesis (Jan Hakkan, 1991; Shaul & Kamal, 1993). The mechanism behind this is that platelets can adhere to and become activated by plaques of atheroma within the vessels. Aggregate form as dimeric fibrinogen molecules bind to platelets bridging adjacent cells. The initial aggregate constitutes the nidus from which intravascular clots are formed, sometimes leading to clinicopathological manifestations of thrombosis.

The concentration of plasma fibrinogen is another strong risk factor for the development of arterial thrombic disorders (Chao-Hung & Shin-Pu, 1995). Epidemiological studies have identified fibrinogen as a major risk factor for myocardial infarction and positive associations with raised fibrinogen concentration have also been reported for thrombotic stroke, transient ischaemic attacks and peripheral arterial diseases.

One important cofactor, which has been associated with thrombosis, is Von Willebrand factor, which acts as a cofactor for Factor VIII. Its function is primarily to stabilise factor VIII and secondly to mediate platelet aggregation and adhesion to vascular endothelium. Von Willebrand factor was first described in bleeding disorder, but later proved to have numerous other roles, some of which can be viewed in terms of pathogenesis of atherosclerosis and thrombosis.

As the level of Von Willebrand factor increases endothelial dysfunction, a condition, which change the ability of the cell to participate adequately in both coagulation and fibrinolysis. Thus it can be said that Von Willebrand is a predisposing factor to atherosclerosis and thrombus formation.

Mauritius is an island where the incidence of smoking and coronary heart diseases is increasing. Since there are no local data pertaining to the effects of smoking on blood haematological markers, the present work was undertaken to measure the levels of different haematological parameters among a random group of habitual smokers.

METHODOLOGY

Based on a questionnaire we have previously designed, one hundred and eighteen (118) male subjects aged between 30-45yr were recruited into the study. Smokers who have been smoking more than 10 cigarettes daily for at least the last 5yr were selected. Upon inclusion into the study and oral informed consent obtained, venepuncture of each subject was performed using 5-ml plastic disposable syringes.

One hundred smokers were matched for age and sex with eighteen strict non-smokers who constituted the control group. Blood was dispensed in 3.2% trisodium citrate and potassium-EDTA coated tubes. For haemostatic tests, blood was collected in 3.2% trisodium citrate tubes and immediately centrifuged at 3000*g* for 5min. The supernatant plasma was used immediately for the haematological tests. Due to limited availability of reagents Cofactor VIII was assayed in 43 subjects only (25 smokers and 18 non-smokers).

Haematology

Haemostatic tests, which included the determination of prothrombin activity, cofactor VIII activity, activated partial thromboplastin time and assay for fibrinogen were performed using commercially available kits (Biomerieux, France). Haemoglobin was measured using Drabkin's reagent and platelet counts were determined microscopically.

Quality control

Uniplasmatrol Normal was used as quality control for the coagulation tests. Before each assay, the lyophilised control was reconstituted and analysed as for sample.

Statistics

Arithmetic mean and standard error of the mean (SEM) were calculated for variables in the smokers and non-smokers. The strength of relations was assessed by linear correlation and P values < 0.05 were taken as significant. All statistics were performed using the SPSS software.

RESULTS

The mean values for the coagulation and haematological parameters and standard errors of the mean including the level of significance of the difference between the smokers and non-smokers are given in Table 1.

Table 1. Coagulation and haematological parameters (mean ± SEM values) in a smoking and non-smoking group

Parameters	Smokers	Non-smokers	Statistics
Prothrombin time (% Activity)	90.2 ! 0.80	91.1 ! 1.36	P>0.05
Activated partial Prothrombin time (sec)	28.1 ! 0.48	32.2 ! 0.76	P>0.05
Fibrinogen level (g/L)	3.61 ! 0.16	3.06 ! 0.07	P<0.05
Cofactor VIII (% activity)	97.7 ! 0.64	102.4 ! 3.01	P>0.05
Haemoglobin (g%)	15.1 ! 0.11	14.7 ! 0.15	P>0.05
Platelets (x 10^9/L)	22.8 ! 5.2	256.8 ! 4.2	P>0.05

Our results showed that fibrinogen level was significantly higher (P<0.05) in the smokers (x = 3.61±0.16 g/L) than in the non-smoking group (x = 3.06 ± 0.07 g/L). Correlation analysis revealed that there was a positive correlation between fibrinogen level and smoking habit.

DISCUSSION

A large series of studies indicate undoubtedly that smoke inhalation, either active (such as smoking cigarettes) or passive (such as breathing indoor smoke), is a potential hazard for daily life and can cause severe lesions to the cardiovascular system.

There is a direct correlation between the level of exposure and morbidity (Leone, 1993). However only few reports mention the direct relationship of smoking to coagulation. Most reports are on coagulation and disease related to thrombosis (Jan Hakkan, 1991; Chao-Hung & Shin-Pu, 1995). These include mostly the heart diseases which apart from smoking, have several different causes such as raised serum lipids, high blood pressure, stress and genetic factors.

Our results indicate that fibrinogen level was significantly higher among smokers than non-smokers adds on to the already available evidence which show that raised fibrinogen concentration is associated with thromboembolic stroke, transient ischaemic attacks, peripheral arterial disease and angina pectoris.

It has been proposed that fibrinogen links platelets receptors, which is a precondition for platelet aggregations and also promote hypercoagulable state as well as causes endothelial damage, disorganisation and dysfunction.

Hence based on our findings one may infer that smokers are more at risks of developing thromboembolic accidents than the non-smokers. We thus recommend that (i) in addition to lipids investigation among subjects at risks of coronary heart diseases, determination of fibrinogen needs to be routinely performed in the biochemistry/ haematology laboratories in Mauritius and (ii) the implementation of a more aggressive anti-smoking campaign especially among the Mauritian youth.

REFERENCES

CAWLEY, J.C. (1983). Haematology; haemostatics. *Integrated Clinical Science*, 53-67.

CHAO-HUNG, H., & SHIN-PU, W. (1995). Haemostatic risk factors of coronary artery disease in the Chinese. *International Journal of Cardiology* **51**, 79-84.

COTELLARO, M. & BOSCHETTI, C. (1992). The PLAT study: Haemostatic function in relation to atherothrombic ischaemic events in vascular disease patients. *Atherosclerosis and Thrombosis* **12**,1063-1069.

JAN HAKKAN, J. (1991). Von Willebrand factor in plasma: a novel risk factor for recurrent myocardial infarction and death. *British Heart Journal* **66**, 351-355.

LEONE, A. (1993). Cardiovascular damage from smoking: a fact or belief? *International Journal of Cardiology* **38**, 113-117.

PENN, A. & CAROLL, A. (1991). Butadine; A vapour phase component of environmental tobacco smoke, accelerates arteriosclerotic plaque development. *Circulation* **93**, 552-556.

SHAUL, M.S. & KAMAL, H. (1993). Red cell fragility in cigarette smokers and its relation to cardiac hypertrophy. *Artherosclerosis* **98**, 91-98.