Effect of long term use of glucocorticoids on coagulation homeostasis

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Abstract

Glucocorticoids are known to be the most effective anti-inflammatory drugs used for a big range of disorders. Glucocorticoids are used orally by about 1% of the adults but their use is associated with side-effects. Glucocorticoid excess has been recognized as a riskfactor for venous thromboembolism (VTE). This study carried out to evaluate the possible effect of long term use of glucocorticoids on coagulation homeostasis represented by prothrombin time (PT) and activated partial thromboplastin time (APTT).The results indicated that both of PT and APTT tests were significantly lower in the glucocorticoid group compared to control group.Beneficial effects of glucocorticoidtreatment in active disease appear to balance probabledirect and adverse effects on coagulation and fibrinolysis.Clinical studies are needed to sufficiently evaluate the risk-benefit of glucocorticoid use per population when thromboticcomplication is the focal point

Key wards:Glucocorticoids, prothrombin time, activated partial thromboplastin time, Haemostasis.

Introduction

Glucocorticoids are known to be the most effective anti-inflammatory or immunosuppressive drugs used for a big range of disorders and have been used as part of the treatment strategy of various obstinate diseases such as rheumatoid arthritis, asthma, atopic dermatitis, inflammatory bowel disease, and cancer as well as transplant rejection(1, 2).Glucocorticoids are used orally by about 1% of the adults but their use is associated with side-effects (3, 4). The risk of cardiovascular disease has been increased, especially with higher doses of glucocorticoids (5, 6).Acute arterial thrombotic events, such as myocardial infarction and stroke are the major contributors to this increase in cardiovascular risk and they are superimposed on the hastened atherosclerosis associated with glucocorticoid excess (7, 8). Furthermore, adding to the cardiovascular morbidity, glucocorticoid excess has been recognized as a risk factor for venous thromboembolism (VTE) (9- 12).

Haemostasis is the process that retains the blood within the vascular system during periods of injury. The coagulation mechanism may be thought of as a complex series of cascading reactions involving development of enzymes from their precursor (zymogens, procoagulantsproenzymes). Most of the substances which are necessary for coagulation are present in an inert form and must be converted to an activated state. As one enzyme is formed it then becomes available to convert the next zymogen to its activated enzyme (serine protease). This process continues until a fibrin meshwork clot has formed. In addition to the zymogens, protein cofactors and membrane phospholipids surfaces, calcium ions play an active role in the final development of the fibrin clot (13). The prothrombin time test (also known as the pro test or PT test) is a useful screening procedure for the extrinsic coagulation mechanism including the common pathway. It detects deficiencies in factor II, V, VII, and X. The prothrombin time test is frequently used to follow oral anticoagulant therapy that inhibit factors II, VII, IX and X. Thromboplastin activates the extrinsic coagulation system in plasma in the presence of calcium ions. The subsequent clotting time is dependent on the

concentration of factors II, V, VII and X. Thus prolongation indicates a deficiency in one or more of these factors (14). The APTT is a global coagulation screening test that is used for assessment of the coagulation status in patients with suspected acquired deficiencies of coagulation factors of the intrinsic and common pathways of the coagulation system. The test is affected by multiple factors, including the levels of factors VIII, IX, XI, XII, X, II, and fibrinogen. The APTT is widely used for monitoring anticoagulation therapy with low levels of heparin (from 0.1 IU/mL to approximately 1 IU/mL). In a normal population, the APTT varies, and this interindividual variability is reflected in a wide reference interval. The APTT reagent is a mixture of phospholipids and activators (eg, kaolin silica, or ellagic acid). Studies have shown considerable differences in the responsiveness of various APTT reagents to mild and moderate deficiencies of coagulation factors, particularly factors VIII and IX (15). Corticosteroids have a prothrombotic effect and would independently contribute to the risk of venous thrombosis in patients with IBS on glucocorticoid therapy (16).

This study aimed at establishing the role of glucocorticoid- induced alterations in anticoagulant and fibrinolytic factors and to evaluate the possible effect of long term use of glucocorticoids on coagulation homeostasis represented by PT and APTT.

Subjects and Methods

This study was conducted during the period from February to March, 2015. Twenty two individuals aged between 20 and 55 years were included in this study and they were divided into two groups. The first group consists of 12 individuals on glucocorticoid therapy for at least 6 months and the second group is a control group consists of 10 normal healthy volunteers. The blood samples were obtained from all individualsincluded in this study using sterile syringes, withdrawn from vein and placed separately in containers containing tri-sodium citrate anticoagulant. Centrifugation was carried out to all samples for 15 minutes at 3000 rpm rateto separate the blood cells from plasma in order to obtain plasma for prothrombin time test. The obtained plasma sample of each individual were poured separately in plane containers

using automatic pipette and freezed till analysis.PT and APTT were assayed through standard clotting methods using BIOLABO Kit, France, according to company instructions.

Statistical analysis:

Statistical analysis was performed usingGraphPad Prism software (version 5.0, GraphPad Software, Inc., San Diego, CA). Unpaired Student's t-test was used and the values were expressed as mean ± S.D.Results with $P < 0.05$ were considered significantly different.

Results

Twenty two individualsaged between 20 and 55 years were divided into two groups. The first group consists of 12 individuals on glucocorticoid therapy for at least 6 months and the second group is a control group consists of 10 normal healthy volunteers and the coagulation parametersPT and APTT were measured for all participants. The results indicated that both of PT and APTT tests were significantly lower in the glucocorticoid group compared to control group.

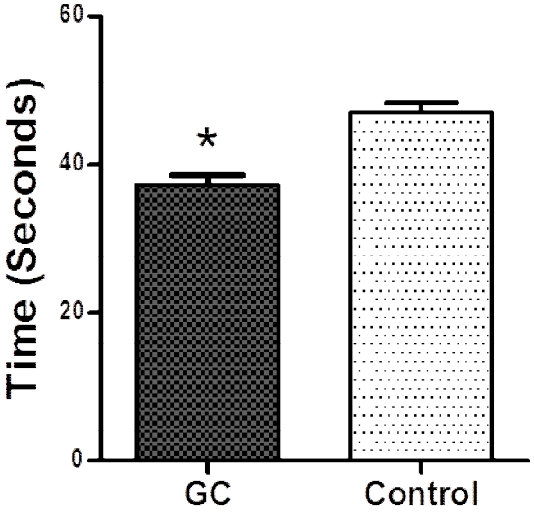

Figure 1:Activated partial thromboplastin time (APTT)values for individuals on glucocorticoid therapy for at least 6 months and the control individuals. Values are expressed as mean ± S.D. *p <0.05 considered as significant.

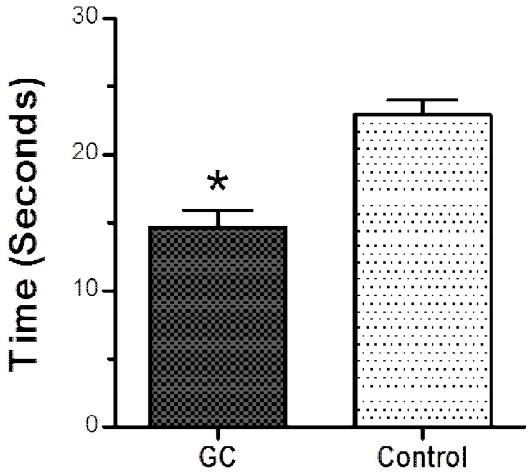

Figure 2: Prothrombin time (PT)values for individuals on glucocorticoid therapy (GC) for at least 6 months and the control individuals. Values are expressed as mean ± S.D. *p <0.05 considered as significant

Discussion and Conclusion

This study aimed at establishing the role of glucocorticoid- induced alterations in anticoagulant and fibrinolytic factors and to evaluate the possible effect of long term use of glucocorticoids on coagulation homeostasis represented by PT and APTT.

The results indicated that both of PT and APTT tests were significantly lower in t glucocorticoid group compared to control group.

Only one study reported a greater number of thrombotic complications in glucocorticoid-treated patientsthan in those free of glucocorticoids (17). Beneficial effects of glucocorticoidtreatment in active disease appear to balance probabledirect and adverse effects on coagulation and fibrinolysis. By itself, the reported risk of thrombotic disease associated withglucocorticoid use most likely relates to the underlying conditionnecessitate glucocorticoid treatment rather than glucocorticoiduse itself. However, the risk-benefit of glucocorticoidsmay differ between populations and ultimateconclusion canonly be obtained from studies investigating clinical outcomes.The effects of glucocorticoidsdepend on the clinical state inwhich it is given,most likely as a result of their disease modifying properties.Moreover, it should be noted that different types, dosages anddurations of the glucocorticoids used, as well as the diversityof the populations investigated may be determinants in theeffects on hemostasis.Clinical studies are needed to sufficiently evaluate the risk-benefit of glucocorticoid use per population when thromboticcomplication is the focal point and further research is needed to clarify thefull spectrum of glucocorticoid actions on coagulation andfibrinolysis.Also, it would be interesting to expand research topopulations with less marked activation of inflammation, suchas patients with chronic obstructive pulmonary disease orcancer patients in need of chemotherapy.

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