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Measurement of Prothrombin Time, Activated Partial Thromboplastin Time and VIII Activity in a Sample of Iraqi Patients with Solid Tumors

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Abstract

Acquired thrombophilia is associated with a considerable risk of thrombosis which is highly encountered in malignancy, where both venous and arterial thromboembolism are not uncommon complications. Patients with malignant tumors, also present with hypercoagulability, even in the lack of thrombosis. Besides, activation of coagulation pathway may play a part in tumor progression. Around 15% of all patients with malignancy develops thrombosis during the course of their disease. Thrombosis can affect the morbidity and mortality of the underlying illness. Furthermore, complications of Thrombosis are one of the most common causes of death in patients with malignant tumors. Therefore, preventing thrombotic complications in cancer patients is a clinically significant concern. To study the effect of solid malignant tumors on blood coagulation via measurements of prothrombin time (PT), activated partial thromboplastin time (APTT) and factor VIII activity. Thirty patients diagnosed with malignant tumors attending the oncology consolatory out-patient clinic at Baghdad teaching hospital were investigated versus a control group of 30 healthy donors. PT, APTT and factor VIII activity were estimated, PT and APTT assessed by semi-automated technique and factor VIII activity was measured by clotting method. PT and APTT results were insignificantly related to control group 13.037 (±0.651) vs. 13.433 (±0.43) respectively. There was a significant correlation between PT with the stage of the malignant tumors. There was statistically significant difference in mean factor VIII activity between the patients and control group ($p < 0.000$). There was increase in factor VIII activity in cancer patients compared to the control group reflecting subclinical thrombophilia and higher risk of Venous thromboembolism (VTE) in patients with solid tumors due to activation of both prothrombotic and fibrinolytic pathways by malignant cells which is vital to consider primary prophylaxis by anticoagulants.

Keywords: Prothrombin time, Activated partial thromboplastin time, Factor VIII, Thrombophilia, Solid tumors

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Introduction

It is estimated that VTE disease occurs in about 6.8% of patients with an underlying malignancy [1, 2, 3]. A constellation of factors rather than a single event contributes to the hypercoagulable state of cancer. Chemotherapy, surgery, immobilization, and the presence of comorbid conditions are associated with increased risk of clotting in these patients. However, the leading factor that predisposes cancer patients to thrombosis seems to be related to the interaction of tumor cells with the hemostatic system. Cancer cells possess a host of procoagulant properties mediated through excessive release of angiogenic factors, cytokine release as well as direct effect on the vessel wall [1, 4].

Thrombotic events can influence the morbidity and mortality of the underlying disease. Thrombotic complications are among the most common causes of death in patients with cancer. Therefore, preventing these complications in cancer patients is a clinically relevant issue. Recently, new approaches to the prevention and cure of thrombosis in cancer have been investigated, and the hypothesis that the strategies to inhibit clotting mechanism may favorably affect malignant disease is gaining increasing interest [2, 5, 6]. The study aimed to assess the effect of solid malignant tumors on blood coagulation via measurements of PT, APTT and factor VIII activity.

Methods

Patients

Over a two-month period, 30 patients (9 males and 21 females) were included and randomly selected in our study, attending the oncology consultatory out-patient clinic at Baghdad Teaching Hospital/ Medical City. All patients were newly diagnosed with malignant solid tumors by reports of histopathology from governmental and private sectors. All the laboratory tests were completed at the hematology and biochemistry departments of The National Center for Teaching Laboratories/Medical City.

Exclusion criteria

All adult patients of age over 60 years, pregnant females or females with history of successive multiple abortions, diabetic and hypertensive, recent major surgery in the last 3 months, signs of active infection (no fever, no malaise, no focus of infection, etc.), on chemotherapy, aspirin and contraceptive pills or with positive history of prior thrombotic event.

Control group

Thirty healthy individuals, matched for sex and age. The subjects age of the control group ranged between 18 - 58 years and both nine males and twenty-one females were involved.

Data collection

Every patient was asked about age, residence, intake of drug including chemotherapy, personal and family history of any thrombotic or suspected thrombotic events, immobility, history of dehydration, leg edema and history of diabetes mellitus or hypertension. Data were obtained from reports of histopathology about the definite histopathological type. malignant tumors Staging were taken from clinical and histopathological reports. ethical approval was acquired from all patients.

Sampling and sample handling

6 ml of blood were collected by a clean aseptic venipuncture from both patient and control group. The taken sample was then divided between three tubes as follows: 1.8 ml of blood in clean disposable capped plastic tube containing 0.2 ml of trisodium citrate dihydrate 109 mmol/l (32 g/l). Platelets poor plasma was obtained after centrifugation of blood at room temperature with 2000 g for 15 min, then 0.5 ml of plasma collected from the upper part of the separated plasma leaving at least 0.5 ml plasma on top of the undisturbed red cell layer and the collected plasma were stored in toppered plastic tubes and frozen at -80 ˚C in deep freeze at the National Blood Transfusion Center for one to two weeks for performing VIII assay. The residual plasma was used for immediate performance of PT and PTT assay within 2 h of blood collection.

Coagulation tests

Manual measurement of PT and APTT tests were done by using (DIAGNOSTICA STAGO/France) kits [7, 8].

PT

The test measures the time of plasma clotting in the existence of an optimal concentration of tissue extract (thromboplastin) and specifies the overall competence of the extrinsic clotting system [9].

APTT

This test measures the clotting time of plasma after the activation of contact factors without tissue thromboplastin addition, and so indicates the overall effectiveness of the intrinsic pathway. The test depends on the contact factors, factors VIII and IX, and on the reaction with factors X, V, prothrombin and fibrinogen [9]. The APTT includes the recalcification of plasma after addition of standardized amount of cephalin (platelet substitute) and a factor XII activator (kaolin) [8].

Factor VIII one stage assay

The one stage assay of factor VIII is grounded on the partial thromboplastin time. The assay compares the ability of dilution of the patient plasma and of standard plasma to correct the partial thromboplastin time of substrate plasma [9]. Normal pooled plasma was calibrated against STA® Unicalibrator (REF 00675) to sustain accuracy of one stage factor VIII assay [10].

Calibration was achieved by making 3 dilutions 1:10, 1:20, 1:40 of both unicalibrator and normal pool plasma, then by addition of 0.1 ml of STAGO-DEFICINT VIII and 0.1 ml of each dilution in plastic tube well mixed and 0.1 ml of cephalin kaolin was added. The mixture incubated for 3 min in water bath at 37 ˚C with gentle tilting every 1 min. Precisely at the end of the 3 min 0.1 ml of pre-warmed calcium chloride 0.025 mol/L added and a stop watch started concurrently to record the clotting time in seconds. The clotting time (APTT) of each dilution of unicalibrator and normal pooled plasma was recorded and plotted on a log paper as factor VIII activity against clotting time in seconds. The clotting times were plotted on a log-log paper to acquire a straight line refers to the parallel line bioassay [10].

Frozen test plasma samples and normal pooled plasma thawed by implementing rapid thawing at 37 ˚C. three dilutions of patient and normal pool plasma in owren koller buffer as follows 1:10, 1:20, 1:40. The test was prepared by putting 0.1 ml of STAGO-DEFICINT VIII and 0.1 ml of each dilution in plastic tube well mixed and after that 0.1 ml of cephalin kaolin was added. The mixture was left for 3 min in water bath at 37 ˚C with gentle tilting every 1 min. Precisely at the end of the 3 min 0.1 ml of pre-warmed calcium chloride 0.025 mol/L was added and a stop watch started concurrently to record the clotting time in seconds. The clotting time (APTT) of each dilution of test and control plasma (normal pooled plasma) was recorded and plotted on a log paper as factor VIII activity against clotting time in seconds [10].

The dilutions were converted to percentage of factor VIII activity and the lowest dilution of the normal pool plasma given a value of 100%. To attain the definite potency of the test sample in terms of control, a horizontal line was drawn from the lowest dilution of the test through both dose response lines to cut the control line, a vertical line then dropped on the concentration axis and the comparative potency of the test sample was read directly of the concentration scale as shown in figure 1. Normal range of factor VIII is 60% - 150% [10].

Statistical analysis

Statistical analysis was performed with Minitab version 15 and Microsoft office excel 2007. Numeric data were analyzed as mean, standard deviation and standard error of the mean, using student

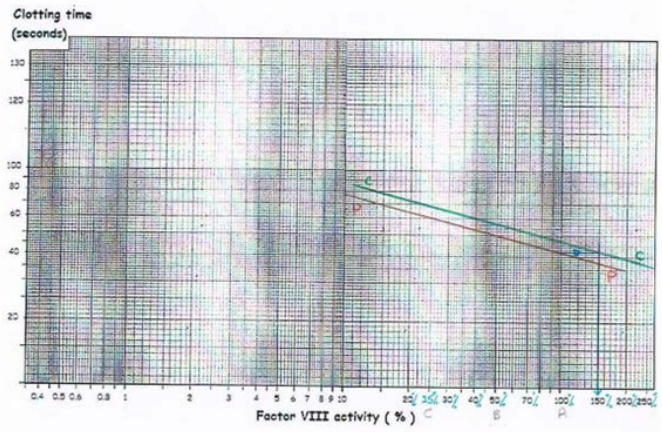

Figure 1: Factor VIII activity.

T-test, while nominal data were expressed as frequencies and were analyzed using chi-square, Pearson correlation was used to determine relation between two numeric variables. P value < 0.05 was considered significant.

Results

The study was conducted on 30 patients (11 males and 19 females) and 30 healthy age and sex matched control subjects (11 males and 19 females).

Clinical data

The mean age for patients' group was 46.9 (±4.5) years and the mean age for the control group was 42 (±3.6) years. The range was (18 - 58) years for both groups. Patients group consisting of 9 males and 21 females control group consisting of 9 males and 21 females. Regarding patients' group the percentages and frequencies of each location of malignant tumor, breast cancer and bronchogenic malignancy were the most frequent malignancy among females and males respectively. Stages' percentages of each malignant tumor with their frequencies are shown in table 1 which reveals that stage two is the most frequent.

Table 1: The percentages of each stage of malignant tumors in patients' group.

Stage	No	%
I	5	16.6
II	9	30
III	8	26.7
IV	8	26.7

Coagulation data

PT and APTT

The mean value of PT level was 13.037 (±0.651) and 13.433 (±0.43) seconds for patient and control groups respectively as shown in table 2. There is insignificant difference in mean PT level between the patient and control group (p = 0.08). The mean value of APTT level was 28.23 (±2.5) and 29.083 (±0.683) seconds for patient and control groups respectively as shown in table 2. There is insignificant difference in mean PT level between the patient and control group (p = 0.08).

Factor VIII activity

The mean value of factor VIII activity was 181% and 99.3% for patient and control groups respectively as shown in table 3, and there is statistically significant difference in mean factor VIII activity between the patients and control group (p < 0.000), as shown in figure 2.

Correlations with stage

There is a negative correlation between PT level and stage of solid malignant tumors which is significant. There is a negative correlation between PTT level and stage of solid malignant tumors but didn't reach statistically significant level. There is a positive correlation between factor VIII activity and stage of malignant tumors which is insignificant (Table 4 and figure 3).

Discussion

Solid malignant tumors are often associated with modification

Table 2: Patient and control groups' results for PT and APTT.

Tests	Mean PT (sec) ± SD	SE	P value
PT patients	13.037 ± (0.651)	0.12	0.08
PT control	13.433 ± (0.43)	0.079	
APTT patients	28.23 ± (2.5)	0.46	0.08
APTT control	29.083 ± (0.638)	0.12	

Table 3: Factor VIII activity results of patient and control groups.

Groups	Mean	SD	SE	P value
Patients	181	58.4	11	0.00
Control	99.3	11.1	2	

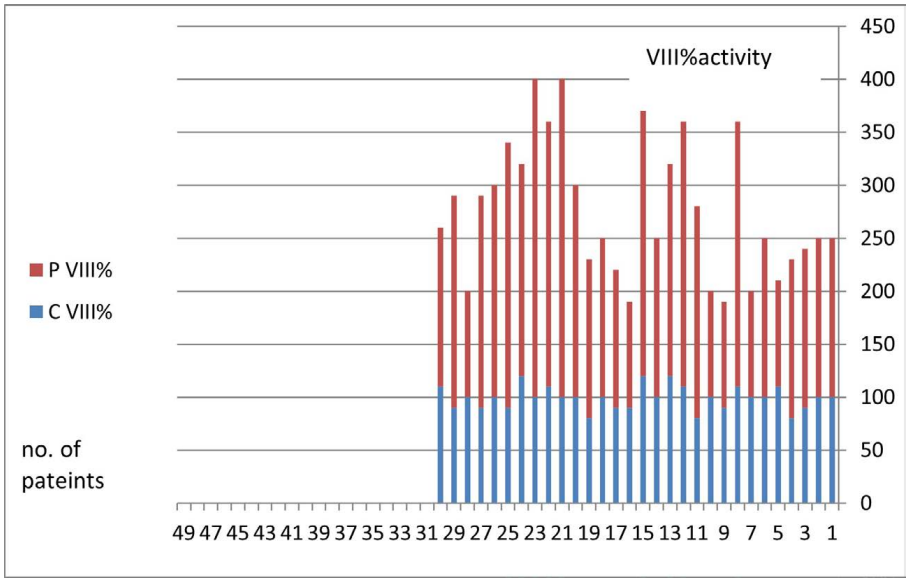

Figure 2: Factor VIII activity for control group (C) and patients' groups (P).

Table 4: Correlation between PT, APTT and factor VIII% with the stage of malignant tumors.

Stages	r	P value
PT	-0.422	0.025
PTT	-0.054	0.781
Factor VIII%	0.167	0.385

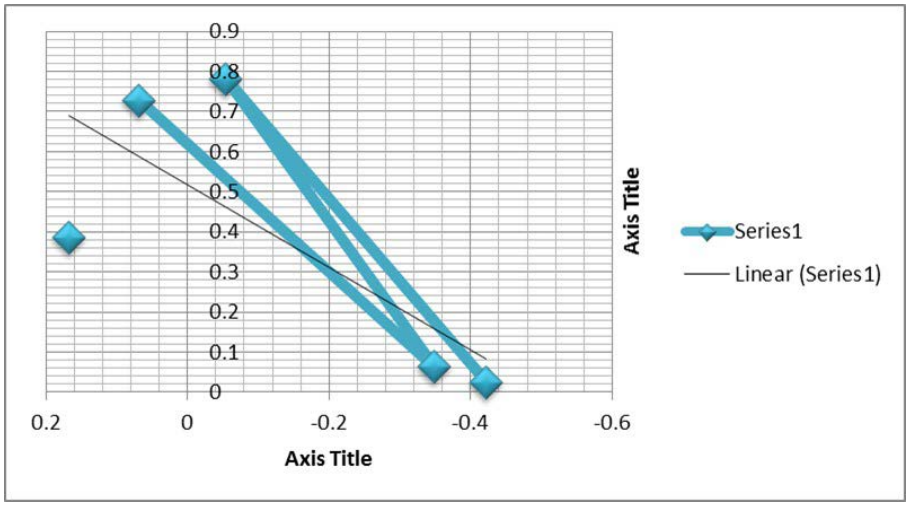

Figure 3: Correlations of coagulation data with the stage of malignant tumors.

of hemostasis and increased thrombotic risk in cancer patients. The mechanism of alteration of hemostasis is still not fully explained but many pathways seem to be involved. Yet, most of patients with malignancy have asymptomatic activation of hemostasis and discovered accidentally by laboratory tests [11, 12].

Hypercoagulability markers are less specific in older age, so in the current study, the age of both control and patient groups were selected below 60 years to avoid misinterpretation [13, 14]. There was significant correlation between PT with the stage of malignant tumor. There were insignificant correlations between APTT and factor VIII with the stage of neoplastic tumors. Ursavaş et al. [15] found that PT, APTT, factor VIII and fibrinogen levels didn't show any statistically significant differences between early and advanced disease groups which agree with the current study except for PT [15].

PT and APTT results of both patients and control groups were comparable, similar results were observed by Micco et al. [11] and Komurcuoglu et al. [16]. Factor VIII activity was significantly higher in patients with solid tumor than control group, similar results were found by Battistelli et al. [17], Lu et al. [18], Yigit et al. [19], and Deitcher and Gomes [20].

Elevated levels of procoagulants released by neoplastic cells leads to increased factor VIII activity associated with VTE risk seem to be persistent and not exclusively attributable to acute-phase response. Factor VIII activity levels above 1.5 IU/ml (150%) are associated with a threefold and a six-fold higher relative risk of VTE when compared with levels below 1.5 IU/ml (150%) and below 1.0 IU/ml (100%), correspondingly. VTE risk is 11-fold higher with factor VIII levels greater than 200% [21].

Conclusion

There was significant elevation in factor VIII activity in patients with neoplastic tumors compared with the control group reflecting subclinical thrombophilia and increased VTE risk in patients with malignancy as a result of activation of prothrombotic and fibrinolytic pathways by neoplastic cells that is extremely necessary to take into consideration primary prophylaxis by anticoagulants.

Acknowledgements

None.

Conflicts of Interest

None.

Ethical Approval

The Medical Ethical Committee of The Baghdad Medical City Complex approved this. Participant consent was waived by the committee since only patient files were reviewed.

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