Original Article

HAEMORHEOLOGICAL CHANGES IN CANCER PATIENTS ON CHEMOTHERAPY

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ABSTRACT

Objective: To assess the rheological changes in haematological and non-haematological cancer patients' pre and post chemotherapy.

Patients and Method: It is a prospective study of 50 patients comprising 16(32%) haematological and 34(68%) non-haematological cancers of various types from March to December 2005 at University of Benin Teaching Hospital, Nigeria. Rheologic parameters estimated by the various specific diagnostic methods were determined in cancer patient's pre and post chemotherapy. The rheological tests estimated were relative plasma viscosity (RPV) measured by means of a capillary viscometer, whole blood viscosity (WBV), erythrocyte sedimentation rate (ESR) and plasma fibrinogen concentration (PFC) estimated by the Ingram's Clot weight method.

Results: The RPV in pre chemotherapy (p=0.006) and WBV in post chemotherapy (p=0.0231) patients measured revealed a significant difference when compared to controls. The fibrinogen concentration (P<0.0001) and ESR values (P<0.0001) were significantly increased in cancer patients when compared to controls.

Conclusion: We conclude that total reduction of hyperviscosity and hyperfibrinogenaemia may contribute to effective treatment strategies in cancer patients.

KEY WORDS: Haemorheology, Cancer, Chemotherapy.

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INTRODUCTION

Blood rheology is the science of the flow and deformation of blood. Clinically, blood rheology is important because circulatory resistance has two major components, vascular and rheological. There is evidence demonstrating that haemorheologic abnormalities and thromboembolic complications occur frequently in patients with malignant disease.[1,2] Factors identified as favoring this are procoagulant and/or fibrinolytic activity of cancer cells, concomitant bacterial infections, surgery, radiotherapy and chemotherapy. Pathophysiologic and technical difficulties have impeded progress in evaluation of the clinical effectiveness of haemorheologic treatment.[3]

Rheologic characteristics of blood depend on the cellular and other plasmatic components. Invivo, this determines the flow properties of the microvascular, macrovascular and submacrovascular dimensions.[4] The study of rheologic mechanisms regulating blood circulation is necessary for successful development of optimal programs for combined treatment of cancer patients.[1] Haemorheological values

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like haematological values of local/native population may differ from developed countries due to specific factors: racial, genetic and geographic conditions. Variations in late presentation of our patients with inadequate response to therapy for the various cancers may also cause rheological changes to differ from our developed countries. Hence, the aim of this study is to assess the changes in rheological values in cancer patients' pre and post chemotherapy and also lack of data on the subject in native Africans justified this study.

PATIENTS AND METHODS

A total of 100 subjects aged 18years and above in a prospective study at the University of Benin Teaching Hospital, Nigeria was studied over a 10 months period (March to December 2005). This comprised of 16(32%) haematological, 34(68%) non-haematological malignancies (Table-I) and 50 controls who were prescreened and found without any history of malignancy /or any disorder. The ethical committee of the Hospital granted approval for this study. The inclusion criteria were based on presence of typical clinical features and specific diagnostic criteria for the various cancers. All the initial tests were carried out prior to any form of blood transfusion. Rheological parameters were estimated in 50 controls and 50 various types of cancer patients' pre and post-chemotherapy monthly on an average of 4 cycles total. The rheological tests estimated were relative plasma viscosity (RPV) measured by means of a capillary viscometer using the method of Reid and Ugwu[5] and whole blood viscosity (WBV). Erythrocyte sedimentation rate (ESR) was measured using the Westerngren method while the haematocrit (Hct) was determined employing the method in Dacie and Lewis.[6] The plasma fibrinogen concentration (PFC) was estimated by the Ingram's Clot weight method.[7] Differences in haemorheological values were estimated by the Mann-Whitney test. GraphPad (instat) Version 2.05a statistical software was used in data analysis.

Table-I: The various types of haematological and non-haematological malignancies seen on admission.

Cancers	*Number (n=50)*	*Frequency (%)*
Haematological (n=16)		
Non Hodgkin's lymphoma	7	43.8
Multiple myeloma	3	18.8
Chronic myeloid leukaemia	2	12.5
Acute lymphoblastic leukaemia	2	12.5
Chronic lymphocytic leukaemia	1	6.25
Hodgkin's lymphoma	1	6.25
Non Haematological (n=34)		
Breast cancer	9	26.5
Carcinoma of the colorectal	5	14.7
Carcinoma head of pancreas	4	11.8
Carcinoma of the oesophagus	3	8.8
Renal tumor	2	5.9
Choriocarcinoma	2	5.9
Malignant melanoma	1	2.9
Nasopharyngeal carcinoma	1	2.9
Prostatic Carcinoma	1	2.9
Dermatofibroma	1	2.9
Neurofibroma	1	2.9
Carcinoma of caecum	1	2.9
Carcinoma of cervix	1	2.9
Liposarcoma	1	2.9
Ductal carcinoma	1	2.9

RESULTS

A total number of 100 subjects used in the prospective study comprised 23 pre chemotherapy cancer patients comprising 8 males and 15 females, 27 post chemotherapy patients comprising 11 males and 16 females and 50 controls comprising of 24 males and 26 females. The haematological malignancies as shown in Table-I comprised 6 males and 10 females with non-Hodgkin's lymphoma (43.8%) and multiple myeloma (18.8%) having the highest frequency. The non-haematological malignancies comprised of 11males and 23 females with breast cancer (26.5%) having the highest frequency. The overall mean age was 46.5±15.4 with a peak age incidence in the 5th decade of life.

Table-II shows the mean (±SD) rheological values between the controls and pre and post chemotherapy patients respectively. From our study the pre and post chemotherapy Hct values was significantly decreased while the ESR was significantly increased when compared with the controls. The RPV was statistically

Table-II: Haemorheological values in controls, pre chemotherapy and post chemotherapy cancer patients.

Variables	*Pre chemotherapy (n=23)*	*Controls (n=50)*	*P values*
Haematocrit (g/dl)	34.13± 7.48	37.62±4.66	0.0173
ESR (mm/1hr)	74.26±36.14	14.98±7.31	0.0001
Plasma viscosity (cp)	1.88±0.56	1.63±0.19	0.0059
Whole blood viscosity (cp)	3.93±0.61	3.90±0.72	ns
Fibrinogen (g/l)	5.13±2.52	2.49±0.59	0.0001
Variables	*Post chemotherapy (n=27)*	*Controls (n=50)*	*P values*
Haematocrit (g/dl)	28.67±7.94	37.62±4.66	0.0001
ESR (mm/hr)	75.80±35.61	14.98±7.31	0.0001
Plasma viscosity (cp)	1.68±0.25	1.63±0.19	ns
Whole blood viscosity (cp)	3.52±0.66	3.90±0.72	0.0231
Fibrinogen (g/l)	5.23±1.89	2.49±0.59	0.0001

*ns- not significant

increased in pre chemotherapy (p=0.0059) while WBV was statistically decreased in post chemotherapy patients (p=0.0231). A significant increase in PFC was also found when compared with the controls (P<0.0001). On comparing the pre and post chemotherapy values there was a significant decrease in Hct (p=0.0164) and WBV (p=0.028) values.

The Haemorheological findings for the haematological and non haematological malignancies subgroups in Table-III when compared with controls showed a significant changes in all the rheological values except WBV which was non significant (p=0.4021). All the haematological malignancies had moderate to marked increase in RPV of >1.8-2.5cp while the non-haematological malignancies had a median value of 1.7cp.

DISCUSSION

The basis for the variations in rheologic parameters under study stems from the fact that cancer cells which damage DNA cells affect the activities of blood vessels.[8] They are said to be useful in the diagnosis of rheological abnormalities as well as to assess the impact of therapeutic cytotoxics drugs being used.[9] Rheological alterations commonly found in malignant disease are mostly pronounced in advanced-stage cancer. The extent of these changes in some cancer types is related with the stage of cancer, prognosis of disease and the patients' risk for thrombosis.[10]

As expected, the pre and post chemotherapy Hct values were significantly decreased when compared to the controls. This is similar to the study of Thompson et al[11] who reported a decrease in Hct in the early stages of cancer and a further decrease post chemotherapy. This decrease is largely due to the toxic nature of the chemotherapeutic agents as well as disease entity itself causing a decrease in erythropoiesis. The significant increase in ESR (P<0.0001) agrees with other studies.[12,13] This increase

Table-III: Haemorheological values between controls, Haematological and non-Haematological cancer patients

Variables	*Haematological (n=16)*	*Non Haematological (n=34)*	*Controls (n=50)*	*P values*
Haematocrit (g/dl)	27.9±3.4	28.9±2.2	37.62±4.66	0.0001
ESR (mm/1hr)	73.8±4	75.8±3	14.98±7.31	0.0001
Plasma viscosity (cp)	1.98±0.6	1.67±0.3	1.63±0.19	0.0010
Whole blood viscosity (cp)	3.74±0.7	3.70±0.7	3.90±0.72	ns
Fibrinogen (g/l)	5.21±2.44	5.22±2.03	2.49±0.59	0.0001
Platelets ($x10^9$/l)	128.2±54	201.2±61	204.6±87	0.0009

could be due to the reduction in Hct and alteration in serum proteins especially in fibrinogen levels.

There was also a significant increase in RPV (P=0.006) in pre chemotherapy patients. There was a tendency towards decrease in RPV in post chemotherapy patients but this is in contrast to the study by Laogun et al[14] who reported an increase in RPV post chemotherapy. This may be due to the relative increase in PFC observed post chemotherapy and not due to the low Hct values. The fact that haematologic and non-haematologic cancers were used/grouped together may have affected the results. This is because different cancers may exhibit different changes in rheology due to production of specific factors/proteins that affect these parameters eg multiple myeloma and production of paraproteins. There was a non-significant slight increase in relative WBV comparing pre chemotherapy cancer patients with controls. The post chemotherapy patients however showed a statistical decrease in WBV (P=0.0231). This decrease could be accounted for by the recorded decrease in Hct and the increase in RPV and ESR values.[15]

The Haemorheological findings for the haematological and non-haematological cancers when compared with controls were significantly higher except for the WBV. This is similar to a study where it was reported that the most frequent constellation in cancer patients is an increase in PV and RBC aggregation that produces hyperviscosity.[10] The aetiology of hyperviscosity syndromes can be due to:[16] a) an increase in total plasma protein levels, or the appearance of a monoclonal protein as found in 6 haematological cancers in the study (3 MM patients, 2 CGL patients and 1 NHL patient) and 10 non haematological cancers (4 breast cancers, 2 each for cancer of rectum, pancreas and cervix). b) the increase in the number of blood cells. The essential problems as seen in leukaemia patients are the hugely elevated white cell count and the mechanical properties of the leucocytes, i.e. their relatively poor deformability and their adhesiveness for the endothelium.[17] c) increase in the erythrocyte's internal viscosity; d) changes in the erythrocyte's viscoelastic properties; e) the excessive aggregating tendency of the erythrocyte's and perhaps that of the platelets. While hyperviscosity may result in ischaemic and thromboembolic episodes, the causes may include cancer, genetic abnormality, infection, metabolic disorders and many others.[18] Hence, not much was discussed with malignancies in this study as other abnormality/disorders are mainly mentioned in earlier published literatures and also due to extreme paucity/lack of published data locally.

The PFC was found to be significantly increased (P<0.0001) in both groups of cancer patients and this was similar to other findings.[10] The observed increase may be as a result of the short half-life of fibrinogen. It is possible that the increase in fibrinogen concentration is a reflection of the overall stress response often accompanying cancer patients. Alternatively, the increase may be due to dehydration. Even the implication of hyperviscosity may result in a hypercoagulable state, a risk factor in the development of fibrin-thrombin formation due to the existing condition, which allows coagulation factors to accumulate. It is well known that plasma viscosity and fibrinogen are markedly increased in various disease conditions- hyperviscosity syndromes.

In conclusion, cancer patient's pre and post chemotherapy were found to have impaired rheological function. Hence, improvements of blood flow by reducing the level of plasma fibrinogen and blood viscosity have to be taken into account seriously for effective treatment strategies in cancer patients. Future research into rheological functions in individual malignancies is advocated as they produce specific factors/proteins, which exhibit different changes in rheology.

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