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Thrombotic Complications Assessment in Polycythemia

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Objective: To study thrombotic complications in polycythemia patients.

Setting: Hematology clinic, Baghdad Teaching Hospital, Iraq.

Design: Prospective study.

Method: The study was performed from October 2001 till January 2005. Full history, physical examination and appropriate investigations were done to patients diagnosed with polycythemia.

Result: Seventy-seven patients enrolled in this study, 52 patients with Polycythemia Vera, 21 with secondary polycythemia and 4 with spurious polycythemia. Thrombotic complications occurred in 17 (32.69%) patients of the Polycythemia Vera group, out of which acute coronary syndrome was seen in 6 (24%), cerebrovascular accidents in 6 (24%), deep vein thrombosis in 5 (20%), mesenteric artery thrombosis in 5 (20%), portal vein thrombosis in one (4%), hepatic vein thrombosis in one (4%) and erythromelalgia in one (4%). In secondary polycythemia only 3 out of 21, (17.64%) had thrombotic complications.

Patients, with secondary polycythemia and PCV higher than 60, had history of thrombosis in one patient (4.76%) only. Finally, no thrombotic complications in spurious polycythemia were seen.

Conclusion: Thrombotic complications in Polycythemia Vera were common and more frequent in patients with higher PCV, raised platelets count and raised white blood cell count. Hypertension was statistically significant predictor of thrombosis in Polycythemia Vera.

Further research using bigger sample size is suggested. Multicentre study would be advised for this purpose.

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Polycythemia Vera (PV) is an acquired myeloproliferative disorder, which causes overproduction of all three hematopoietic cell lines, most prominently the red blood cells[1].

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Most patients present with symptoms related to expanded blood volume and increased blood viscosity. Common complaints include headache, dizziness, tinnitus, blurred vision, and fatigue. Generalized prurities, especially following a warm shower or bath is an occasional symptom. Sixty percent of patients are men, and the median age at presentation is 60 years. Physical examination reveals plethora and engorged retinal veins. The spleen is palpable in 75% of cases, but is nearly always enlarged when imaged. Thrombosis is the most common complication of Polycythemia Vera and the major cause of morbidity and death in this disorder[1].

Venous or arterial thrombosis is common in patients with Polycythemia Vera, and is related to an increase in blood viscosity and platelet number and/or activity. A prior major thrombotic complication e.g. cerebrovascular, myocardial infarction, superficial thrombophlebitis, deep vein thrombosis, pulmonary embolism was present in 15 percent of patients entering into the PVSG study[2].

Major thrombotic events can occur in patients who otherwise have few clinical and laboratory features of PV. Examples include the Budd-Chiari syndrome, and portal, splenic, or mesenteric vein thrombosis, in which the ensuing portal hypertension and hypersplenism may mask the increase in blood cell counts[2,3].

The other criteria for diagnosis such as serum erythropoietin, endogenous erythroid colony formation and JAK2 mutation have high specificity, but the sensitivities are not high enough to detect early stages of PV[4].

Survival in Polycythemia Vera is compromised primarily as the result of increased whole blood viscosity with median survival for 18 months in an untreated patients and 10 to 15 years in treated patients[5]. Thrombocytosis is a common finding in chronic myeloproliferative diseases. Thromboembolic complication is a cause to an increased morbidity and mortality[6].

Thrombotic complications are also attributable, in part, to qualitative and quantitative platelet abnormalities, and to the presence of leukocytosis[2,7-9].

Advanced age, prior thrombosis and high hemoglobin were statistically significant risk factors of thrombotic events[10]. Thromboembolic risk suggests that myelosuppressive therapy should be used in older patients with higher risk of vascular events[11].

Patients with Polycythemia Vera have JAK2 (cytosolic tyrosine kinase) mutation an increased risk of vascular thrombosis caused by an increased red blood cell (RBC) mass and platelet activation[12].

The aim of this research is to study thrombotic complications in polycythemia patients.

METHOD

The study was performed from October 2001 till January 2005 at the hematology clinic, Baghdad teaching hospital, Iraq.

Full history and physical examination were performed to all patients referred to the clinic with PCV higher than 52. History of thrombotic complications was documented.

Full blood count using MS 9 electronic counter including PCV, WBC and platelets count were measured. To differentiates Polycythemia Vera group from secondary Polycythemia and spurious Polycythemia the following investigations were done: oxygen saturation using pulse oximetry, pulmonary function tests, red cell measurement, bone marrow biopsy and ultra sound examination to the abdomen. New thrombotic complications during the study were documented.

Diagnosis was made using criteria developed by the Polycythemia Vera Study Group[13].

Major Criteria:
A1 Raised red cell mass (RCM), male $\geq$ 36 ml/kg, female $\geq$ 32 ml/kg
A2 Normal arterial oxygen saturation $\geq$ 92%
A3 Splenomegaly

Minor Criteria:
B1 Platelet count > 400 x 109/l
B2 White blood cell count (WBC) > 12 x 109/l
B3 Leukocyte alkaline phosphatases > 100
B4 Serum B12 > 900 pg/ml or unbound B12 binding capacity > 220 pg/ml

Diagnosis:
A1 + A2 + A3 establishes Polycythemia Vera
A1 + A2 + two of category B establishes Polycythemia Vera
Data analysis was performed using Fisher's exact test through Graph pad software /Quick Calcs online calculator for scientist:
http://www.graphpad.com/quickcalcs/contingency2.cfm/

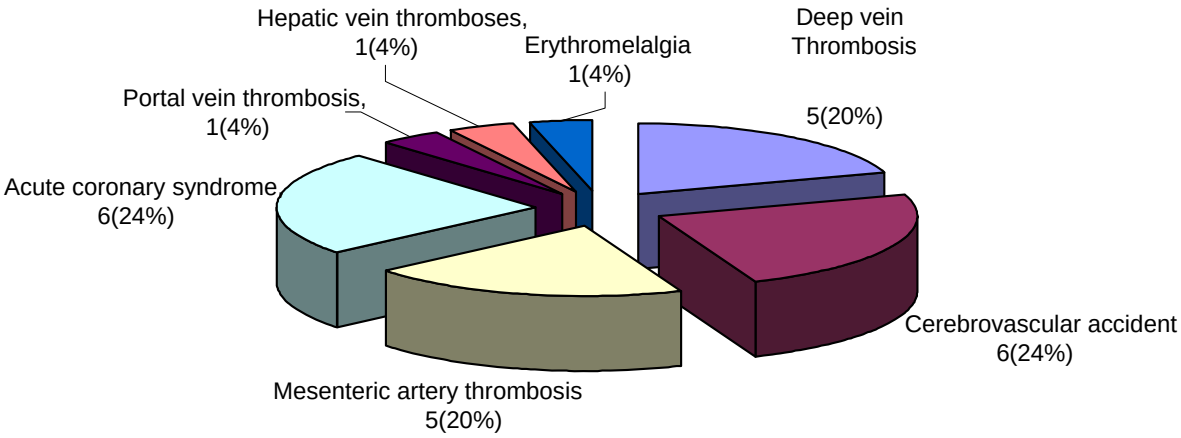
RESULT

Fifty-two patients had Polycythemia Vera, 21 had secondary Polycythemia and 4 with spurious Polycythemia. Male to female ratio was 1:1 in Polycythemia Vera group. The most common symptoms in Polycythemia Vera patients were headache, pruritus, dizziness and weight lose in almost 60%, sweating, visual symptoms and weakness in nearly 50%. The least presenting symptoms were paraesthesia in 30% and gout in 16%. Diabetes mellitus presented in 7 patients (13.46%) while hypertension in 10 patients (19.23%). The spleen was palpable in 83% but the liver in 34% in Polycythemia Vera patients, see Table 1.

Table 1: Polycythemia Vera (n=52) Symptoms and Signs Percentages

Symptoms or Signs	Number	Percentage
Headache	33	63.46%
Weakness	25	48.07%
Purities	32	61.53%
Dizziness	32	61.53%
Sweating	28	53.84%
Visual symptoms	28	53.84%
Weight lose	31	59.62%
Paresthesia	16	30.76%
Joint Symptoms	9	17.30%
Liver Enlargement(palpable)	18	34.61%
Spleen Palpable	43	82.69%
Male	26	50%
Female	26	50%
Hypertension	10	19.23%
Diabetes mellitus	7	13.46%

In Polycythemia Vera group, thrombotic complications occurred in 17 patients (32.69%), out of which acute coronary syndrome was seen in 6 patients (24%), cerebrovascular accidents in 6 patients (24%), deep vein thrombosis in 5 patients (20%), mesenteric artery thromboses in 5 patients (20%), portal vein thromboses in one patient (4%), hepatic vein thromboses in one patient (4%) and erythromelalgia in one patient (4%), see Table 2 and Graph 1. Some patients had more than one complication; therefore, the total complications seen in the 17 patients were 25.



Graph 1: Seventeen Patients of Polycythemia Vera Had Twenty-Five Thrombotic Complications

Table 2: Thrombotic Complications Types in Polycythemia

Thrombotic complications types	Number of patients with Polycythemia Vera (n=52)	Number of patients in secondary Polycythemia(n=21)
Acute coronary syndrome	6	3
Deep vein thrombosis	5	0
Cerebrovascular accidents	6	0
Portal vein thrombosis	1	0
Hepatic vein thromboses	1	0
Mesenteric artery thrombosis	5	0
Erythromelalgia	1	0
Patients with more than one thrombotic events	3	0
Total no of thrombotic Patients	17	3

In Polycythemia Vera group, the thrombotic complications were frequently seen in patients with packed cell volume (PCV) higher than 60, white blood cells more than 15,000 per microliter and platelets more than 400,000 per microliter. High PCV was seen in 8 (15.09%); raised white blood cells was seen in 10 (18.86%) and raised platelets count was seen 11 (21.15%). Most patients who had complications were middle aged; only one patient (3.86%) was more than 60 years old. However, three patients (17.64%) had more than one thrombotic complication. In Polycythemia Vera group, diabetes mellitus was associated with thrombotic complications in 2 (11.76%), while hypertension was associated with thrombotic complications in 7 (41.17%).

Hypertension was, stastically significant, predictor for thrombotic complications in Polycythemia Vera group patients, see Table 3.

Table 3: Relationships between Thrombotic Complications and Thrombotic Predictors in PV Patients

	Total	PCV>60	WBC >15000	Platelets >400000	Diabetes mellitus	Hypertension
Polycythemia Vera	52	25	31	39	7	10
Thrombotic complications	17	8	10	11	2	7*

*****The association between hypertension and thrombosis is considered to be very statistically significant p=0.0090

In secondary Polycythemia, 3 patients (14.28%) had acute coronary syndrome, all had hypertension, but no history of diabetes mellitus .One patient (4.76%) had PCV more than 60 in secondary Polycythemia group. There were no raised platelets or raised white blood cell counts in secondary Polycythemia.

No thrombotic complications in spurious Polycythemia were seen.

DISCUSSION

In this study, there was an increased risk of thrombotic accidents in Polycythemia Vera compared with other types of polycythemia.

In Polycythemia Vera, patients with PCV more than 60, platelets more than 400000 per microliter and WBC more than 15000 per microliter, patients are more likely to have thrombotic complications.

Hypertension and diabetes mellitus are associated with thrombotic vascular complications with variable ratio. Age was associated with thrombosis but to lesser extent than previous two factors. Hypertension was statistically significant predictor of thrombosis in Polycythemia Vera.

In this study, only one complication of acute coronary syndrome was found in secondary Polycythemia.

Many studies have found that age $\geq$ 60, a total white blood cell count >15,000 per microliter and platelets count more than 400,000 per microliter were associated with thrombotic risk in Polycythemia Vera patients[2,14,15].

In some studies, it showed that the presence of the JAK2V617F mutation is associated with an increased thromboembolic complications[16].

Myelosuppressive therapy, preferentially with hydroxyurea, can reduce the rate of vascular complications, but there is some concern about an increased rate of leukemic transformation with this agent[17].

In this study, the number of patients is small to reach statistical significance. Further studies with bigger number of patients is highly recommended

CONCLUSION

Thrombotic complications in Polycythemia Vera were common in patients with higher PCV, high platelets count and high white blood cell count. Hypertension was the only factor statistically related to thrombosis in Polycythemia Vera.

Further studies with bigger number of patients taking other coagulation events predictors are recommended. Multicentric study would be advised for this purpose.

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