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ORIGINAL ARTICLE

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Hemorrhagic and thrombotic complications in patients with myeloproliferative diseases

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Objective: To correlate the incidence of hemorrhage and thrombosis to bleeding time (BT) and platelet aggregation in 27 consecutive patients with myeloproliferative diseases (MPD). **Design:** Retrospective study. **Setting:** Public tertiary referral center. **Patients:** Eighteen patients with chronic myelogenous leukemia (CML), 5 with polycytemia vera (PV), 2 with essential thrombocytemia (ET) and 2 with idiopathic myelofibrosis (MF). Duke's BT and epinephrine-induced platelet aggregation were performed on the patients and on 10 healthy individuals. **Results:** Eleven patients presented symptoms (41%): 9 with hemorrhage (33%) and 5 with thrombosis (19%). There were less symptomatic patients in the CML group (28%) than in the other MPD (67%), without statistical significance (Fisher, p=0.06). Duke's BT was longer in symptomatic patients (Mann-Whitney, p<0.05). Platelet aggregation was abnormal in 7 patients (26%) and 71% of them were symptomatic (Fisher, p = 0.07).
Conclusions: The high incidence of bleeding and thrombosis in patients with MPD was related to prolonged BT, but not to platelet aggregation abnormalities.

UNITERMS: Myeloproliferative Diseases. Hemorrhage. Thrombosis. Bleeding time. Platelet aggregation.

INTRODUCTION

Both hemorrhagic and thrombotic episodes account for the morbidity and mortality in myeloproliferative diseases (MPD)[1]. Either phenomena may be related to acquired platelet abnormalities observed in some patients, such as increased platelet production or destruction, altered platelet secretory granular content, changes in glycoprotein concentrations and abnormal response to aggregating agents, especially epinephrine. The incidence of all these platelet abnormalities in patients with MPD has been published in a comprehensive review of 124 studies by Holme et al.[2].

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The aim of this study was to verify the incidence of thrombotic or hemorrhagic complications in patients with MPD, followed up for a 2 year period, and to correlate them to the bleeding time and platelet aggregation induced by epinephrine.

MATERIAL AND METHODS

Patients

The authors evaluated 27 consecutive patients with MPD attending the Hematology Department of UNIFESP. There were 18 patients with chronic myelogenous leukemia (CML), 5 with polycytemia vera (PV), 2 with essential thrombocytemia (ET), and 2 with idiopathic myelofibrosis (MF). Diagnosis was established according to standard criteria considering blood cell count, peripheral blood smear analysis, bone marrow aspiration and biopsy, blood and plasma volume studies, leukocyte alkaline phosphatase

score and cytogenetic study[3]. Patients' ages ranged from 16 to 75 years (average = 56 years), and there were 11 men and 16 women. All of them were evaluated as outpatients. Patients were being treated with either hydroxyurea or bussulfan as chemotherapy. Only one patient, who had a transitory ischemic attack, was taking aspirin, which was discontinued 10 days before blood sampling. Ten healthy individuals, 7 women and 3 men, from the laboratory staff constituted the control group. Their age ranged from 27 to 69 years (average = 38 years).

Methods

Blood cell counts were performed automatically in a Coulter counter and platelet counts were made in Neubauer chambers, with phase microscopy.

Bleeding time was performed according to Duke's technique, and consisted of a small incision in the earlobe using a sterile lancet. The cut was blotted every 30 seconds with filter paper until bleeding stopped. Results were recorded in minutes[4].

Platelet aggregation study was performed on platelet rich plasma (PRP) obtained from citrated whole blood, using a Minigator II - Payton Scientific Aggregometer, according to Bohr[5]. Platelet count on PRP was adjusted to 300 x 10^9/L. Epinephrine was used as an aggregating agent at a final concentration of 2.2 mM. Normal individuals presented two aggregation waves and this was considered to be the normal pattern. Patients were classified as having an abnormal aggregation pattern when there was either a single wave or a complete absence of aggregation. All patients were evaluated on two occasions, at least one month apart, and were considered abnormal only when they presented the abnormal pattern in both analysis. To evaluate the assay conditions, blood from healthy volunteers was collected daily as a control.

The frequency of symptomatic and asymptomatic patients, as well as the frequencies of normal and abnormal platelet aggregation patterns, were compared using the Fisher exact test. The Mann-Whitney test was used to compare bleeding time in patients and controls.

RESULTS

Eleven out of the 27 patients (41%) had thrombohemorrhagic manifestations: 6 presented hemorrhage, 2 presented thrombosis and 3 presented both features. Patient distribution according to the type of MPD and the occurrence of hemorrhage or thrombosis is shown in Table 1. The CML group presented a lower incidence of symptomatic patients (28%), compared to the other MPD (67%) [PV (80%); MF (50%); ET (50%)], but this difference did not reach statistical significance (Fisher test, p=0.06). Hemorrhage was presented as spontaneous ecchymoses in 3 patients, gingival bleeding in 2, epistaxis in 4, gastrointestinal bleeding in 2, and retinal hemorrhage in 1. Thrombotic episodes included: deep vein thrombosis in 2 patients, transitory ischemic attack in 1, ischemic cerebral attack in 1, and acute arterial occlusion in the absence of arterial disease in 1.

Table 1
Patient distribution according to the myeloproliferative disease, and the presence of hemorrhage or thrombosis

MPD	Asymptomatic Patients	Symptomatic Patients			
	N%	Hemorrhage N	Thrombosis N	Both N	Total N %
CML	13 (72%)	3	0	2	5 (28%)
PV	1 (20%)	2	1	1	4 (80%)
ET	1 (50%)	1	0	0	1 (50%)
MF	1 (50%)	0	1	0	1 (50%)
TOTAL	16 (59%)	6 (22%)	2 (8%)	3 (11%)	11(41%)

(MPD= myeloproliferative diseases, CML= chronic myelogenous leukemia, PV= polycythemia vera, ET= essential thrombocythemia, MF= myelofibrosis).

Mean Duke's BT was 1.8 minutes (min) in patients and 1.3 min in controls and this difference was not statistically significant (Mann-Whitney test, p>0.05). Symptomatic patients had longer Duke's BT (mean ± SD=2.2 ± 1.0min) than asymptomatic (mean ± SD=1.6 ± 0.81min) and controls (mean ± SD=1.3 ± 0.53min), but a statistically significant difference was seen only between symptomatic patients and controls (Mann-Whitney test, p<0.05) (Figure 1).

Platelet aggregation pattern was abnormal in 7 patients (26%): 5 out of 18 with CML (28%), 1 out of 2 with ET (50%), and 1 out of 2 with MF(50%). All patients with PV had normal platelet aggregation (Table 2). No difference was seen between the frequency of abnormal platelet aggregation in the CML group, compared to the other MPD (Fisher test, p=0.57).

Symptomatic patients had a higher incidence of abnormal platelet aggregation patterns (46%) than

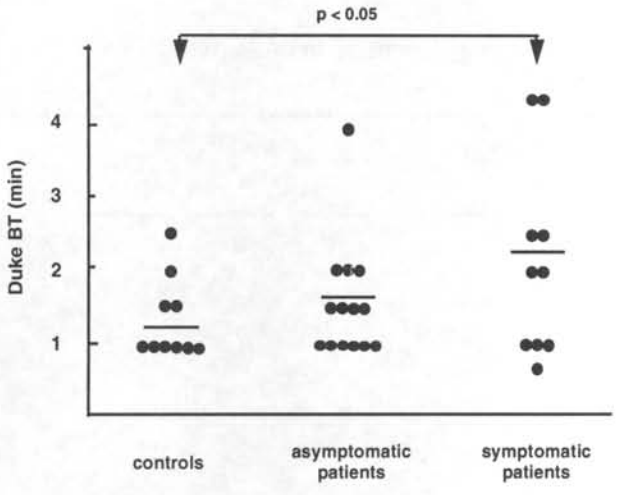

Figure 1 - Duke's bleeding time in patients and controls.

Table 2
Results of platelet counts, bleeding time and platelet aggregation according to myeloproliferative disease

Diagnóstic	Platelet count (x10⁹/L)	Bleeding Time (min)	Platelet Aggregation
CML	250	1.5	Abnormal
	400	2.5	Abnormal
	200	1.0	Normal
	180	1.0	Normal
	150	1.0	Normal
	200	1.5	Normal
	210	ND	Normal
	350	1.0	Normal
	200	1.0	Abnormal
	430	4.0	Normal
	140	ND	Normal
	300	1.0	Abnormal
	100	4.0	Abnormal
	400	1.5	Normal
	200	2.0	Normal
	280	2.5	Normal
PV	260	1.0	Normal
	210	2.0	Normal
	200	2.5	Normal
	320	2.0	Normal
	90	4.0	Normal
MF	200	1.0	Normal
	1000	ND	Abnormal
ET	1000	1.5	Abnormal
	680	2.0	Normal

(ND= not done, MPD= myeloproliferative diseases, CML= chronic myelogenous leukemia, PV= polycythemia vera, ET= essential thrombocythemia, MF= myelofibrosis)

asymptomatic ones (13%), but this difference did not reach statistical significance (Fischer test, p=0.07).

There was no significant difference between Duke's BT in patients with abnormal platelet aggregation (mean ± SD=2.0 ± 1.0min) and those with normal patterns (mean ± SD=1.8 ± 0.95 min) (Mann-Whitney test, p>0.05).

DISCUSSION

The frequency of thrombohemorrhagic complications in MPD varies in different studies, and some reported data are presented in table 3. The authors observed a higher incidence of hemorrhage (33%) than thrombosis (19%), in 27 patients with MPD. Similar findings have been reported by Adams et al.[6], Walsh et al.[16], and Bush et al.[7], who studied 21, 16 and 72 patients with MPD, respectively. However, Barbui et al.[12] in a large series of 101 patients observed that the incidence of hemorrhage and thrombosis were similar, whereas Zucker et al. found that thrombosis was more common[11].

The relatively lower incidence of hemorrhage in patients with CML, compared to other MPD, was also observed by other authors[7, 15]. As pointed out by Schafer[1], cutaneous and mucous membrane were the most common sites of bleeding.

Duke's BT was longer in symptomatic patients, compared to asymptomatic ones and controls. In fact, the occurrence of prolonged bleeding time was reported by some authors, but in no case was there a positive correlation between BT and the presence of hemorrhage[13, 15, 16]. BT is an "in vivo" measuring of primary hemostasis, that depends not only on platelet function, but also on complex interactions among platelets, subendothelium, and von Willebrand factor[17]. The prolonged BT in patients who presented hemostatic complications suggests that these individuals may have an altered platelet/endothelium interaction that could favor the occurrence of thrombosis or hemorrhage.

A prolonged Duke's BT correlates with hemostatic defects that are clinically relevant, probably better than does the Ivy BT, which may be prolonged even in asymptomatic patients[18].

Table 3
Frequency of hemorrhage, thrombosis and abnormal platelet aggregation in patients with MPD (NS=not stated)

Author	N	Hemorrhage (%)	Thrombosis (%)	Altered Platelet Aggregation (%)
Zucker (11), 1972	12	25	33	32
Adams (6), 1974	21	29	0	76
Ginsburg (9), 1975	19	16	26	62
Walsh (8), 1977	16	19	12,5	75
Waddell (10), 1981	18	11	17	NS
Barbui (12), 1983	101	11	10	39
Buss (7), 1985	72	36	14	NS
Raman (13), 1989	43	16	16	56
Present study, 1994	27	33	19	26

The frequency of abnormal platelet aggregation induced by epinephrine ranged from 32% to 76% in the reported series (Table 3). This great variability could be due to the epinephrine concentrations used in the different assays. In the present study, abnormal platelet aggregation was observed in only 26% of the 27 patients, maybe because the patients were considered abnormal only when they present the alteration on two different occasions.

Some authors reported altered platelet aggregation induced by other agents, such as ADP and collagen, although the incidence of low responsiveness to epinephrine has been the most common finding in these studies[13,20].

71% of patients with abnormal and 30% with normal platelet aggregation were symptomatic, but no statistical difference was seen. Therefore platelet aggregation pattern seems not to predict the occurrence of bleeding in patients with MPD, as observed by others[10,15,19].

In conclusion, the authors observed a high incidence (41%) of bleeding or thrombotic events in 27 patients with MPD. Duke's BT could discriminate the symptomatic patients, while platelet aggregation induced by epinephrine proved to be useless for this purpose.

RESUMO

Objetivos: Relacionar a incidência de sintomas trombo-hemorrágicos com tempo de sangramento (TS) e agregação plaquetária em pacientes com doenças mieloproliferativas crônicas (DMP). **Desenho:** Estudo retrospectivo. **Local:** Hospital público terciário - UNIFESP-EPM. **Participantes:** Vinte e sete pacientes ambulatoriais, consecutivos, com DMP. Estudado TS de Duke e agregação plaquetária induzida pela adrenalina, comparando a 10 indivíduos saudáveis. **Mensuração:** Análise estatística, com nível de significância menor ou igual a 5% (p<= 0.05). **Resultados:** Onze pacientes sintomáticos (41%) : 9 com hemorragia (33%) e 5 com trombose (19%). Os pacientes com leucemia mielóide crônica apresentaram menos sintomas (28%) que os portadores de outras DMP (67%), sem significância estatística (Fisher, p=0,06). O TS de Duke foi maior em pacientes sintomáticos (Mann-Whitney, p<0,05). Agregação plaquetária anormal em 7 pacientes (26%), sendo 71% sintomáticos (Fisher, p=0.07). **Conclusões:** A incidência de hemorragia ou trombose nos pacientes com DMP foi relacionada com TS prolongado mas não com alterações na agregação plaquetária.

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