Early predictors of haemorrhage in acute febrile syndrome patients from Bucaramanga, Colombia: a dengue endemic area

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ABSTRACT

Introduction: Spontaneous haemorrhage is an important cause of hospitalisation in dengue patients. Early predictors of these complications could help to make opportune decisions.

Methods: We prospectively evaluated 51 febrile patients (without previous spontaneous haemorrhage), including 32 cases of dengue fever. Initial evaluation was performed during the first 96 hours after the onset of fever and included complete blood cell count and coagulation tests. Participants were followed-up daily until the seventh day of the disease.

Results: Overall, 15 patients developed spontaneous haemorrhage during the follow-up. Tourniquet test and dengue infection were not associated with haemorrhage (p-value is greater than 0.2). In a logistic regression analysis, platelet count (odds-ratio [OR] 0.78; 95 percent confidence interval [CI] 0.65–0.94) and partial thromboplastin time (OR 1.78; 95 percent CI 1.06–2.99) were independently associated with spontaneous haemorrhage.

Conclusion: Early alterations in platelet count and coagulation test could predict spontaneous bleeding in the acute febrile syndrome.

Keywords: acute febrile syndrome, dengue fever, dengue haemorrhagic fever, platelet count alteration, spontaneous haemorrhage

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INTRODUCTION

Dengue virus infection, which is endemic in many parts of Asia and the Americas, is a major public health issue in the tropical world.[1] Each year, an estimated 100 million cases of dengue fever (DF) occur, and between 250,000 and 500,000 cases are reported as dengue haemorrhagic fever (DHF) due to the simultaneous presence of haemorrhagic manifestations, thrombocytopenia and signs of plasma leakage.[1] Classification in DF and DHF groups has been criticised because many patients with serious complications (including death) do not meet all criteria of severity.[2] Typically, patients who require hospitalisation due to spontaneous bleeding, deep thrombocytopenia or hypotension, do not show plasma leakage signs, such as haemoconcentration. Therefore, it is necessary to consider each complication as separate components that require medical intervention.

In addition, it would be useful to have tools for prediction of complications, such as spontaneous haemorrhage, which have been associated with increased mortality and necessity of complex procedures.[3,4] These tools should be able to detect early stages of the disease, even before dengue diagnosis is available. Previous studies have reported associations between haemorrhage and other manifestations such as thrombocytopenia, coagulation alterations, and low arterial pressure.[5-9] However, these associations have not been prospectively documented. Consequently, this cohort study aimed to identify early manifestations that can predict spontaneous haemorrhage in patients with acute febrile syndrome from a dengue-endemic area.

METHODS

A prospective study was undertaken at the metropolitan area of Bucaramanga, Colombia, from April to December 2003. Patients with unspecified febrile syndrome were enrolled from two health institutes (Centro de Salud "El Rosario" and Fundación Oftalmológica de Santander – Clínica Carlos Ardila Lulle). Only patients who were febrile for 96 hours of disease or less were included in the study. Individuals with spontaneous bleeding (before enrolment), immunosuppression or chronic disease, were excluded.

Information on clinical manifestations was directly obtained from the patients through standardised interview, physical examination and blood sample, which was taken during the first evaluation. Complete blood cell count and determination of prothrombin time (PT) and partial thromboplastin time (PTT) were done at admission. Patients were followed-up on a daily basis until the seventh day of disease, in order to identify spontaneous bleeding. Serum samples were obtained twice: one before 96 hours of disease (acute phase) and one after the seventh day (convalescent period). Serum specimens were tested for the presence of dengue-specific antibodies using a modified enzyme-linked immunosorbent assay

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Table I. Haemorrhage according to status of dengue infection.*

Specific site of bleeding	Dengue infection (n = 32) (%)	Other febrile illness (n = 19) (%)	p-value
Bleeding from gums	2 (6.3)	0	0.27
Epistaxis	1 (3.1)	1 (5.3)	0.70
Petechiae, ecchymoses	5 (15.6)	0	0.07
Gastrointestinal bleeding	3 (9.4)	2 (10.5)	0.89
Genital haemorrhage	1 (3.1)	0	0.44
Other haemorrhages	3 (9.4)	1 (5.3)	0.60
Total	11 (34.4)	4 (21.1)	0.31

* The haemorrhage was documented during the follow-up on patients without previous bleeding.

Table II. Early manifestations associated to spontaneous bleeding in patients with unapparent febrile syndrome.

Variable*	Total (n = 51)	Bleeding (n = 15)	No bleeding (n = 36)	p-value
PT (s)	15.1 ± 0.8	15.6 ± 0.6	15 ± 0.8	0.01 †
PTT (s)	32.7 ± 2.3	34 ± 1.3	32.2 ± 2.4	0.02 †
Platelet count ($\times 10^3/\mu L$)	177.3 ± 73.3	146 ± 51.1	190.3 ± 77.8	0.04 †
White blood cell count (/μL)	4049 ± 1584	4227 ± 1926	3975 ± 1443	0.61
Physical findings				
Fever (≥ 38°C)	11 (21.6)	3 (20)	8 (22.2)	0.86
SAP (mmHg)	114.5 ± 15.5	109 ± 14.4	116.9 ± 15.5	0.10
DAP (mmHg)	69.9 ± 11	65.6 ± 12.8	71.6 ± 9.8	0.07
CR	80.2 ± 15	80.3 ± 11.7	80.1 ± 16.4	0.97
Tourniquet test	10 (20)	2 (13.3)	8/35 (22.9)	0.44

* Data is expressed as mean ± standard deviation or no. (%).

† Values considered statistically significant.

PT: prothrombin time; PTT: partial tromboplastin time; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; CR: cardiac rate

(ELISA).[10] In addition, viral isolation was performed in acute serum samples using C6/36 cultures. According to the WHO criteria, dengue infection was defined by viral isolation or increasing titres of antibodies in paired serum samples.

Statistical analysis was performed using STATA software, version 9.0 (Stata Corp, College Station, TX, USA). The two-sample *t*-test and the χ^2 test were used to examine differences in demographic and clinical characteristics between case patients and control subjects, and to assess potential confounding variables. Multivariate analysis was performed in order to find a model where all the covariates included have a significant association with spontaneous bleeding. A strategy of manual backward selection was used, starting with the model including all covariates that were significant on univariate analysis. At each step, the most nonsignificant covariate (based on Wald statistics) was removed from the model. After that, to find a model conforming only to significant covariates, omitted covariates were each added back into the model one by one and kept, if significant. In this multivariate analysis, platelet count and coagulation time were included as continuous variables.

RESULTS

Overall, 63 patients were evaluated, with 12 of them being excluded for presenting with bleeding before enrolment. Of the other 51 patients, 15 (29.4%) developed spontaneous haemorrhage during the follow-up. Among these patients, dengue infection was confirmed in 32 out of the 51 patients (62.7%), but spontaneous bleeding was not more frequent in this group compared with non-dengue patients. Moreover, bleeding in specific sites was similar between DF and other febrile illnesses (Table I). Patients who developed spontaneous haemorrhage exhibited a slight prolongation of PT and PTT, as well as low platelet count, compared with patients with no bleeding (Table II). Tourniquet test was not associated with a higher risk for haemorrhagic complications. Moreover, other early clinical findings were not statistically significant between bleeding and non-bleeding groups. In multivariate analysis, only platelet count and PTT were statistically associated with outcome. Thus, platelet count was negatively associated with the incidence of haemorrhage, with an odds-ratio (OR) of 0.78 for each increasing of 10.000/μL (95% confidence interval [CI] = 0.65–0.94). On the other hand, PTT prolongation was positively associated with spontaneous bleeding (OR = 1.78; 95% CI = 1.06–2.99). Inclusion of PT in that model was not associated with the outcome (OR = 1.55; 95% CI = 0.4 –5.8).

DISCUSSION

Available studies about the prediction of spontaneous bleeding in dengue patients have only included those with a clinical diagnosis of dengue infection or in a late stage of disease.[5-8] However, in medical practice, it may be difficult to differentiate between DF and any other causes of inapparent febrile illness during the first days.[11] Therefore, it is important to evaluate prognostic factors in the early stages of the disease, independently of the actual condition of infection. Consequently, this report

shows a prospective evaluation of potential predictors of spontaneous bleeding, which could be employed in patients presenting with acute febrile syndrome from a dengue-endemic area.

According to the results, some patients (12/63) presented with spontaneous haemorrhage in the first four days of disease; however, most of these complications appeared after this period. Interestingly, patients who developed haemorrhage during the follow-up, exhibited early differences in coagulation tests and platelet count, which could help to predict this outcome. These findings are consistent with previous retrospective studies where diverse alterations in coagulation factors, as well as deep thrombocytopenia, have been associated with haemorrhagic complications of DF.[6-9] For example, deep thrombocytopenia (≤ 50.000 platelets/μL) was associated with spontaneous haemorrhage in a cross-sectional study, which included 790 hospitalised dengue patients (OR = 2.2; 95% CI = 1.5–3.1).[9] Furthermore, in other retrospective studies, hospitalised children with spontaneous bleeding exhibited lower platelet count compared with those without this complication.[6,7] On the other hand, three previous studies reported associations between bleeding and prolongation of PT and PTT.[6-8] Therefore, our findings were consistent with the retrospective evidence and suggested that PTT prolongation and low platelet count could be early predictors of spontaneous haemorrhage in patients with acute febrile illness compatible with DF. However, coagulation tests and platelet count must be widely evaluated in order to establish cut-off for medical interventions.

Positive results from the tourniquet test have been reported significantly more frequently in dengue patients compared to those with other acute febrile illnesses; therefore it has been proposed as a tool for the clinical diagnosis of dengue.[12,13] On the other hand, WHO has recommended that this test be considered for a haemorrhagic manifestation in the classification of severity. However, the tourniquet test is a very unspecific tool for classification of DHF and DF patients.[5] Moreover, our results suggest that the tourniquet test is not an early predictor of spontaneous haemorrhage. In fact, a positive tourniquet test was less frequent in patients with spontaneous haemorrhage. Although this difference was not statistically significant, it is paradoxical and we recommend that it be evaluated with a greater number of patients.

Other clinical manifestations were not associated with haemorrhage. Among these manifestations, we evaluated physical findings, such as diastolic and systolic arterial pressure, which were lower in patients with spontaneous bleeding, compared with those without the outcome. Although this difference was nonsignificant, it could be explained by an insufficient sample size. Therefore, we recommend including the measurements of arterial pressure in future evaluations of potential predictors of haemorrhage in this population.

In conclusion, spontaneous bleeding is a frequent complication in febrile patients from a dengue-endemic area. However, some simple laboratory tests, such as platelet count and PTT, when measured in the first days of disease, may predict these complications. These findings could facilitate decision-making in emergency rooms in order to prevent or treat major haemorrhagic complications in time. Additional studies are necessary to confirm our results in different populations, establish cut-off points for decision-making and identify other possible predictors.

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