THROMBOCYTOPENIA IN SEPSIS: A PREDICTOR OF MORTALITY IN THE INTENSIVE CARE UNIT

K H Lee, K P Hui, W C Tan

ABSTRACT

Disseminated intravascular coagulation (DIC) and thrombocytopenia are well-known complications of sepsis, but the relationship between these coagulation abnormalities and outcome have not been well documented. We studied the incidence of thrombocytopenia and DIC in our Medical Intensive Care Unit, and evaluated their usefulness as prognostic risk factors for mortality. Platelet count was not found to be an independent risk factor associated with overall mortality in the 107 patients studied.

In the sub-group of 53 patients with sepsis, 22 (42%) developed DIC, 31 (58%) developed thrombocytopenia (<150,000 x 10^9/L) and 27 (51%) died. Thrombocytopenia was associated with presence of DIC (p=0.003), but not with the type of infecting organism. The platelet count in non-survivors (mean±sem, 97±18x10^9/L) was significantly lower than survivors (194±27x10^9/L, p<0.005). Multiple regression analysis showed that thrombocytopenia was a risk factor for mortality, independent of the APACHE II score. The presence of DIC surprisingly was not an independent risk factor.

We conclude that DIC and thrombocytopenia are common in our adult Medical Intensive Care patients with sepsis, but only the latter is a prognostic factor in addition to the APACHE II score. The incidence of DIC in our patients (mainly Chinese) seems to be more than that of 10 to 20% reported in other series of Caucasian patients. We would, therefore, like to emphasise the importance of platelet count as an prognostic risk factor in sepsis.

Keywords: thrombocytopenia, disseminated intravascular coagulation (DIC), APACHE II, prognostic factor

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INTRODUCTION

Disseminated intravascular coagulation (DIC) and thrombocytopenia have been well described in patients with severe sepsis. Cell wall components from gram-negative organisms (endotoxin)[1,2] and gram-positive organisms (peptidoglycans from *Staphylococcus aureus*)[3] can lead directly to disseminated intravascular coagulation in animal models. Excessive activation of the clotting cascades leads to disseminated intravascular coagulation, causing platelet consumption and thrombocytopenia. During severe sepsis, microvascular endothelium may be damaged by a number of other factors, including poor tissue perfusion, hypoxia, stasis and acidosis. As a result of endothelial damage, platelet adheres to exposed collagen, leading to secondary platelet activation, aggregation and consumption. In sepsis, it is likely that a series of complex interactions lead to the common end-point of thrombocytopenia.

The development of thrombocytopenia and the presence of DIC as markers of outcome in septic patients have not been elucidated. We therefore investigated the importance of these factors in our group of septic patients admitted to the Medical Intensive Care Unit.

METHOD

From June 1991, all patients who were admitted to the Medical Intensive Care Unit were recruited into a prospective study of illness severity scoring with the APACHE II system[4]. From this cohort, 107 patients (53 patients with infection) were analysed retrospectively for the relationship between clotting abnormalities, APACHE II, and sepsis.

Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

K H Lee, MRCP(UK)
Senior Resident

K P Hui, DM
Teaching Fellow

W C Tan, MRCP(UK) FRACP(Aust), FAMS, MD(Aberdeen), FRCP(Edin)
Associate Professor

Correspondence to: Dr K H Lee

Infection was diagnosed in the presence of the following features: pyrexia (temp>38°C), compatible clinical findings and positive blood culture or positive imaging. Sepsis related DIC was considered to be present when D-dimer and fibrin soluble monomer complex (FSMC) were both detected in the absence of other known causes (such as acute liver failure, leukaemia). Patients with other causes of thrombocytopenia (such as leukaemia, chemotherapy of idiopathic thrombocytopenic purpura) who developed an infection were also excluded from analysis. Mortality was defined as death during stay in the Medical Intensive Care Unit.

Statistics

Comparisons between any 2 groups were by unpaired t-test. Associations between proportions and outcomes were tested with chi-square. Multiple regression analysis of independent predictors for mortality were carried out with SAS system (Version 6.1, SAS Institute Inc, North Carolina). Results were presented as mean standard error of mean (sem) unless otherwise stated.

Table I - Characteristics of septic and non-septic patients

	None-septic	Septic
Number	54	53
Age	50±2	54±3
APACHE II score	19±2	21±1.0
Platelet count (x10^9/L)	226±17	144±17*
DIC positive	9	22

* p<0.005 comparing septic and non-septic patients.

RESULTS

Of the 107 patients, 53 patients had sepsis. Chinese (75%) was the predominant race with Malays (17%), Indians (7%), and others (1%) making up the remainder. The septic group had similar APACHE II scores and ages compared to the non-septic goup (Table I). The septic group had significantly lower platelet counts than in the non-septic group (Table II). The median age of the patients with sepsis was 55 (range 18 to 84), with 25 males (47%) and 27 (51%) of patients died. Culture showed gram-negative organisms in 47% and gram-positive organisms in 19% of the patients. The effect of the different organisms on DIC status, the presence of thrombocytopenia,

Table II - Characteristics of survivors and non-survivors of patients with sepsis

	Septic	
	Survivors	Non-survivors
Number	29	24
Age	54±4	54±3
APACHE II score	15±1.0	27±2**
Platelet count (x10^9/L)	194±27	97±18**
DIC positive	7	15

**p<0.005 comparing survivors and non-survivors

and mortality are displayed in Table III. There are no significant difference within the groups for these parameters. Thrombocytopenia (platelet count <150x10^9/L) alone was found in 14 (25%), thrombocytopenia with DIC was found in 17 (32%), and DIC alone was found in 5 (9%) of patients with sepsis. Platelet count was lower in DIC-positive patients than DIC-negative patients (192±25x10^9/L, 77±13x10^9/L respectively, p=0.0006). As expected, non-survivor had higher APACHE II score than survivors in the septic group (27±2 versus 15±1 respectively, p=0.0006), and platelet count was lower in non-survivors than survivors (97±18x10^9/L, 194±27x10^9/L respectively, p=0.004)(Table II). Multiple regression analysis showed that in addition to APACHE II score, platelet count was an independent risk factor for mortality (p<0.05) for the septic patients. Although DIC status was associated with lower platelet count, it was not an independent risk factor for mortality.

DISCUSSION

Our results derived from intensive care patients have shown that thrombocytopenia (57%) and DIC (35%) are common findings in sepsis. Furthermore, thrombocytopenia, but not the presence of DIC, is a prognostic factor independent of APACHE II score that is specific to sepsis.

DIC and thrombocytopenia had been recognised as complications of severe sepsis since the 1950's[5,6]. Nevertheless, no previous study had specifically examined the effects of these abnormalities on outcome. Earlier studies discussed selected patients, usually paediatric[7] or post-surgical[8] patients, who were selected for the presence of coagulation abnormalities. Other studies examined the association between coagulation abnormalities and mortality as a minor part of the main study[9,10].

Platelet count was one of the many physiological variables used in APACHE I[11], but was not included in the later APACHE II[12] and III[13] scoring systems. Knaus and colleagues, in their discussion of the development of APACHE II, excluded platelet count (and other APACHE I variables) as these variables did not appear to improve prognostic prediction. In our intensive care patients, we found that thrombocytopenia was not an independent predictor of mortality in the whole group, but only in the sub-group with sepsis. It was surprising that the presence of DIC was not an independent risk factor for mortality. This may be because DIC is one of several predisposing factors that contribute to thrombocytopenia (see introduction).

Most studies found that DIC is less frequently recorded than thrombocytopenia in sepsis. An earlier study in surgical patients with several bacterial infection documented only an incidence of 10% for thrombocytopenia[14]. Kreger and colleagues found an incidence of 11% of patients with gram-negative sepsis[15]. In the recently published study of the monoclonal anti-endotoxin antibody, HA-1A, DIC was found in about 20% of the group of patients with gram-negative sepsis. In our study, evidence of DIC was found in nearly 40%

Table III -Coagulation profiles and outcome of patients grouped according to infectious organisms

	Gram-negative	Gram-positive	Culture-negative
Number	23	11	15
DIC positive	11	5	5
Thrombocytopenia	167±26	108±38	130±19
Mortality (n)	11	6	8

There was no significant difference amongst the three groups for any of the variables shown.

of our septic patients, about twice as often as the reported incidence. The explanation for this phenomenon is unknown. It is possible that there may be a genetic predisposition, as our patients were mainly Chinese, with smaller percentages of Malays and Indians, whereas the previously published series presumably were mostly Caucasians. We are not aware of the incidence of DIC from the other Asian countries with a predominantly Chinese population.

The increased mortality in our septic patients with thrombocytopenia reflected the severity of sepsis rather than death directly due to thrombocytopenia. Clinically significant blood loss as a result of thrombocytopenia was uncommon in our group of patients. All patients received stress ulcer prophylaxis and platelet transfusion in severe cases (<20,000x10^9/L). Death in our septic patients were commonly due to multiple organ failure. Thrombocytopenia tends to appear early in the course of sepsis, and invariably by the third day after the onset of sepsis, and commonly before the appearance of multi-organ failure.

In conclusion, thrombocytopenia is an independent predictor for death in septic patients, and is an useful adjunct to the more complicated APACHE II scoring system.

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