DIAGNOSING DISSEMINATED INTRAVASCULAR COAGULATION IN ACUTE INFECTION : CAN WE DO WITHOUT FDP & D-DIMER

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ABSTRACT

Alterations in coagulation profile viz. platelet count, prothrombin time (PT), partial thromboplastin time with kaolin (PTTK), thrombin time (TT) and fibrinogen were studied in 96 patients (73 males and 23 females) of acute infections. Fibrin/fibrinogen degradation products (FDP) level >25µg fibrinogen equivalent unit (FEU)/ml along-with D-dimer >1.0µg FEU/ml was considered criteria for diagnosis of disseminated intravascular coagulation (DIC). Normal values were established using plasma from 12 healthy voluntary blood donors. Out of these 96 patients, 15 had infection with Gram positive bacteria, 23 with Gram negative bacteria and 38 with Dengue. In 20 patients, nature of infection was not defined. Mean platelet count per cubic millimetre was 2.14 lac in Gram positive infection and 1.74 lac in Gram negative infection ($p=0.07$). There was no significant difference in other coagulation parameters in Gram positive and Gram negative infection. Platelet counts were low in 71% of Dengue patients but there was no significant alteration in PT, PTTK and TT. None of the Dengue patients had hypofibrinogenemia or DIC though hyperfibrinogenemia was present in 21% of Dengue patients. 20 patients had features of septicemia (Gram +ve 7, Gram -ve 8, undefined 5); 10 had concomitant DIC. DIC was present in additional 4 patients of acute infection without septicemia. PTTK was raised in 60% of the septicemia patients. 20 out of 82 non-DIC acute infection patients had subnormal PTTK. Commonest alteration in 14 DIC patients was raised PTTK with a sensitivity of 78.6% and specificity of 81.7%. Low fibrinogen levels though specific for DIC, were present in only 21.4% of the DIC patients. Combinations of PTTK >38 sec with PT >15 sec or platelet count < 1.5 lac/mm³ were good screening tests for DIC and detected 11 and 10 patients out of 14 with three and two false positives respectively.

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KEY WORDS : D-dimer; Disseminated Intravascular Coagulation; Fibrinogen degradation products; Partial thromboplastin time; Prothrombin time; Thrombin time.

Introduction

Despite a number of studies on coagulation parameters in fulminant septicemia [1-3]; experimental infection [4-6]; and DIC [7-9]; there is a paucity of literature regarding coagulation abnormalities in uncomplicated acute infection. Abnormalities ranging from a rapidly fatal DIC to a slight elevation in the levels of fibrin/fibrinogen degradation products (FDP) are seen in acute infections and septicemia. DIC is a clinical disorder manifested by haemorrhagic diathesis. Pathogenetic mechanisms include activation of coagulation, intravascular consumption of clotting factors and activation of fibrinolytic system. Acute infections caused by various Gram positive and Gram negative microorganisms, viruses, rickettsia, fungi and protozoa play a significant role in pathogenesis of this syndrome. Haemostatic criteria used for diagnosis of DIC include

thrombocytopenia, hypofibrinogenemia, depletion of factor V & VIII and excessive levels of split products (FDPs & D-dimer) [6]. DIC being rapidly fatal there is a need to define infection associated alterations in coagulation profile that detect subset of patients at high risk of developing DIC before the process is irreversible.

Material & Methods

96 patients admitted to Army Hospital (R&R) Delhi Cantt with acute infection were evaluated, either on admission or at the first sign of infection, before definitive treatment. Prothrombin time (PT), kaolin activated partial thromboplastin time (PTTK), thrombin time (TT), plasma fibrinogen level and hemogram including platelet count and peripheral smear were evaluated. Fibrinolytic activity was assessed by FDPs and D-dimer estimation. Relevant clinical features were recorded.

Samples for coagulation studies were collected in siliconized vacutainers containing 3.2% (0.109M) trisodium citrate as anticoagulant (1 vol. for adding 9 vol. of blood) and were processed within 4 hours. PT, PTTK, TT and Fibrinogen titres were done

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TABLE 1
Proportion of patients (%) having abnormalities in coagulation parameters

Category	Platelets < 1.5 lac/mm ³	PT > 15 sec	PTTK		TT > 22 sec	Fibrinogen < 150 mg/dl
			> 38 sec	≤ 23 sec		
All patients (n) = 96	48	20.8	27.0	20.8	16.6	4.2
Gram +ve infection (n) = 15	6.6	26.7	33.3	33.3	26.6	13.3
Gram -ve infection (n) = 23	43.4	39.1	43.5	26.0	17.3	8.7
Dengue fever (n) = 38	71.0	5.3	13.2	15.8	10.5	0
Undefined infection (n) = 20	42.1	26.3	31.5	15.7	21.0	0
Septicaemia (n) = 20	45	50	60	25	30	15
DIC (n) = 14	64.3	64.3	78.5	0	50	21.4
*p values	< 0.001	< 0.05	< 0.05	< 0.05	> 0.05	< 0.05

* p values between Gram +ve, Gram -ve, Dengue and undefined infection.

using commercially available (Sigma) reagent kits and electromagnetic impedance coagulometer (Stago-4, Diagnostica Stago, France). Fibrinogen was estimated by coagulation assay. FDP by staphylococcal clumping and D-dimer by latex agglutination (semi-quantitative). Platelet-counts were done manually using Neubauer chamber and were validated on peripheral smear. Normal values were established using plasma from 12 healthy voluntary blood donors (mean age 27.5 years, 9 males and 3 females). Coagulation control plasma, normal as well as abnormal, was used for quality control.

Acute infection was diagnosed on the basis of clinical features along with positive microbiological or serological evidence. Septicemia was suspected when any two of the following were present : (i) Temp >38°C or <36°C (ii) Total leucocyte count <4000/mm³ or >12,000/mm³ (iii) Unexplained tachypnoea-respiratory rate > 20 per min (iv) Unexplained tachycardia-heart rate >90/min. Patients with positive blood culture or those who had all the four indicators were included in septicemia group [5]. DIC was suspected when more than one of the following criteria were present : (i) Platelet count <1,50,000/mm³ (ii) Fibrinogen <150 mg/dl (iii) PT >6 sec above control (iv) PTTK >10 sec above control (v) TT >10 sec above control [10]. DIC was confirmed if FDPs were 25µg FEU/ml and D-dimer was >1.0µg FEU/ml [10]. The clinical features specifically looked for diagnosing DIC were bleeding, shock, renal, hepatic or respiratory dysfunction and thromboembolic phenomenon [6,8,9].

Statistically it was a cross-sectional study in which causative factor (infection) and effect (coagulation abnormalities) were studied at a given point of time. The data was analysed using Epi-Info-5, statistical package for computerised analysis (CDC Atlanta, World Health Organisation).

Results

Normal values for various parameters, mean and standard deviation (SD), were : platelet count 2.69 (0.69) lac/mm³, PT 12.01 (1.00) sec, PTTK 31.42 (2.47) sec, TT 17.25 (1.29) sec, Fibrinogen 298.92 (51.3) mg/dl, FDPs 2.67 (1.16) µg FEU/ml and D-dimer < 0.5 µg FEU/ml.

Out of the 96 patients there were 73 males and 23 females. The mean age of the patient group was 33.49 years (SD 15.7 years). 15 had infection with Gram positive bacteria and 23 with Gram negative bacteria. During the period of study there was an epidemic of Dengue and 38 patients belonged to that. 20 patients had acute febrile illness in which definite pathogen could not be established. 20 patients had features of septicemia (Gram +ve 7, Gram -ve 8, undefined 5); 10 having concomitant DIC.

Mean age of septicemia patients was higher than non-septicemia (p<0.05). Differences in mean age amongst other sub groups were not significant (p>0.05).

Coagulation parameters in the patient group

Gram positive infections had a mean platelet count of 2.14 lac/mm³ while Gram negative infections had a count of 1.74 lac/mm³ (p=0.07). Mean platelet count of patients of Dengue fever was 1.03 lac/mm³. Mean platelet count of patients having septicemia was 1.45 lac/mm³ and of patients having DIC, 1.35 lac/mm³. Analysed differently, 6.6% of the patients of Gram positive infection, 43.4% of Gram negative infection, 71.0% of Dengue patients and 45% of septicemia had platelet counts <1.5 lac/mm³ (p<0.001) (Table 1). Out of the 14 patients of DIC, 9 had platelet count <1.5 lac/mm³ and 4 between 1.5 and 2.0 lac/mm³. Compared to non DIC patients the difference was not significant (>0.05). In Dengue haemorrhagic fever thrombocytopenia is a disease defining criteria, when these epidemic patients were excluded the differences between DIC and non-DIC patients became highly significant (p<0.01) (Table-2).

TABLE 2

Coagulation parameters in DIC v/s no DIC : no of patients with abnormal result

Parameter	DIC present	DIC absent	Total	Statistical values	
Platelet count					
≥ 2.0 lac/mm ³	1	21	22	Chi Sq	2.7
1.5-2.0 lac/mm ³	4	24	28	Df	2
< 1.5 lac/mm ³	9	37	46	p	> 0.05*
PT					
> 15 sec	9	11	20	Chi Sq (Yates)	15.81
≤ 15 sec	5	71	76	Df	1
				p	< 0.001
PTTK					
24-38 sec	3	47	50	Chi Sq	22.42
≤ 23 sec	0	20	20	Df	2
> 38 sec	11	15	26	p	< 0.01
TT					
> 22 sec	7	9	16	Chi Sq (Yates)	10.45
≤ 22 sec	7	73	80	Df	1
				p	< 0.01
Fibrinogen					
< 150 mg/dl	3	1	4	Chi Sq	27.5
150-200 mg/dl	5	4	9	Df	2
≥ 200 mg/dl	6	77	83	p	< 0.01

* When Dengue fever patients were excluded p value was < 0.01

More than half of the septicemia and DIC patients had high PT and PTTK ($p < 0.05$) (Table-1). Interestingly, subnormal (23 sec or less) PTTK was observed in many acute infection patients but none of DIC patients. Differences in proportion of patients having abnormal result between DIC and non DIC patients for PT, PTTK and TT were highly significant (Table 2). Mean PTTK value of patients having Gram positive infection was 33.40 sec; Gram negative infection 36.69 sec; Dengue fever 31.29 sec; septicemia 43.15 sec and DIC 52.29 sec ($p > 0.05$). Differences in mean values and proportion of patients with abnormal results of various coagulation parameters between Gram positive and Gram negative infection were not significant. Fibrinogen levels below 150 mg/dl were found in 3 and between 151 and 200 mg/dl in 5 of DIC patients ($p < 0.01$) (Table 1&2).

FDP were assessed when there was clinical suspicion of DIC or when more than one parameter out of PT, PTTK, TT, platelet and fibrinogen were abnormal. Out of the 40 patients in whom FDP levels were estimated, 25 had levels $> 10 \mu\text{g}$ FEU/ml. D-dimer was tested in all these patients and in 20 of them the levels were $> 0.5 \mu\text{g}$ FEU/ml.

Between Dengue fever and control group, except platelet count, no other coagulation parameter revealed any significant difference. 8 out of 38 patients of Dengue had fibrinogen levels $> 400 \text{mg/dl}$ compared to 4 out of 58 non Dengue patients.

Out of 14 patients having laboratory indicators of DIC, 8 had bleeding manifestations and 2 had hypotension. 4 had Gram positive infection, 5 had Gram negative infection and in 5 nature of infection was not known. 2 of the patients with Gram negative infection had DIC without clinical features of septicemia (Table-3). Gram positive and Gram negative septicemia were analysed

TABLE 3
DIC and septicemia in non-Dengue acute infection

	Septicaemia	No septicaemia	Total
Gram +ve infection			
DIC	4	0	4
No DIC	3	8	11
Gram -ve infection			
DIC	3	2	5
No DIC	5	13	18
Undefined infection			
DIC	3	2	5
No DIC	2	13	15
Total	20	38	58

TABLE 4
Efficiency of various parameters for diagnosis of DIC in patients suffering from acute infections

	Platelet < 1.50 lac/mm^3	PT > 15 sec	PTTK > 38 sec	TT > 22 sec	Fibrinogen < 150 mg/dl	FDP > $10 \mu\text{g/FEU/ml}$	FDP > $25 \mu\text{g/FEU/ml}$
Positivity in Non DIC	37/82	11/82	15/82	9/82	1/82	11/26	2/26
Positivity in DIC	9/14	9/14	11/14	7/14	3/14	14/14	14/14
Sensitivity	64.3	64.3	78.6	50.0	21.4	100*	100*
Specificity	54.8	86.5	81.7	89.0	98.7	57.6	92.3
PV+	19.5	45.0	42.3	43.7	75.0	56.0	87.5
PV-	90.0	93.4	95.7	91.2	88.0	100.0*	100.0*

* - Laboratory criteria of DIC was FDP $> 25 \mu\text{g/FEU/ml}$ and D-dimer $> 1 \mu\text{g/FEU/ml}$; PV+ - Predictive value of positive test; PV-ve - Predictive value of negative test

as regard to positivity of FDPs and D-dimer as an indication of their proneness to develop DIC. 4 out of 7 Gram positive, and 3 out of 8 Gram negative septicemia patients had FDP $> 25 \mu\text{g}$ FEU/ml and D-dimer $> 1.0 \mu\text{g}$ FEU/ml ($p > 0.05$).

Efficiency of various coagulation parameters for diagnosis of DIC

Out of platelet count, PT, PTTK, TT and fibrinogen, the PTTK at a cut-off of 38 sec provided best diagnostic sensitivity of 78.6% and specificity of 81.7%. Fibrinogen levels at a cut off of $< 150 \text{mg/dl}$ had good specificity (98.7%) but very poor sensitivity (21.4%) (Table-4). Data was further analysed to detect which combinations of the coagulation parameters provide best sensitivity and specificity for diagnosis of DIC in acute infection. Patients of Dengue fever epidemic were excluded as these are not routinely encountered in clinical practice and also because DIC is rare in Dengue [11]. A combination of PTTK $> 38 \text{ sec}$ and PT $> 15 \text{ sec}$ could detect 11 out of 14 DIC patients with a false positivity of 3 out of 44 non-DIC patients. A combination of PTTK $> 38 \text{ sec}$ with platelet count $< 1.5 \text{ lac/mm}^3$ detected 10 out of 14 DIC patients with 2 false positives out of 44 non-DIC patients. Combinations of fibrinogen $< 150 \text{mg/dl}$ with platelet count $< 1.5 \text{ lac/mm}^3$ or PTTK $> 38 \text{ sec}$ were not sensitive and detected only 2 and 3 patients respectively with one false positive each.

Discussion

Infection and coagulation abnormalities

In 68 out of these 96 (71%) patients, one or other coagulation parameter was abnormal. Thrombocytopenia was present in 48%. When 38 patients of Dengue where thrombocytopenia is a disease defining criteria were excluded, prevalence dropped to 32.8%.

Corrigan et al [1] had reported thrombocytopenia in 21 out of 36 (58%) patients of fulminant septicemia compared to 45% in our series. Damaged vascular surface, endotoxin, exotoxin, platelet activating factors or the micro-organisms directly may be responsible for the platelet damage. Circulating platelet levels may be reduced due to deposition within fibrin plug, adherence to injured endothelium and possibly due to pulmonary and hepatic sequestration. Other possible mechanisms that may contribute to thrombocytopenia in infection include antibiotic administration and uraemia [6]. In a study of 45 episodes of septic shock from 83 episodes of bacteraemia, coagulation abnormalities

were observed in 78% and DIC in 24% [2]. In another study of 68 patients [3] with various degree of infection, it was observed that intensive infection and multisystem organ failure (MSOF) was associated with increased PT, PTTK, FDP and D-dimer alongwith decrease in fibrinogen and platelets. DIC was present in 79.7% patients of MSOF. In our series, DIC was present in 50% of those having septicaemia. 4 others had DIC without septicaemia (Table-3). Coagulation abnormalities ranged from 4.2% in fibrinogen to 48.0% in platelets in overall series and from 15% in fibrinogen to 60% in PTTK in septicaemia. One interesting observation was decrease in PTTK (Table-1). Attar et al also reported decreased coagulation time and increased fibrinogen in early stage followed by reversal in late stage in 30 patients of Gram negative infection [12]. More recently, increased levels of thrombin-anti-thrombin III complexes, factor VII, VIIIC, VIII Rwf, fibrinogen and factor XIII have been reported in sepsis [13]. It is likely that the patients reflecting low PTTK were sampled in the early procoagulant phase before going into consumption coagulopathy.

Gram positive v/s Gram negative infection

One of the earliest reports implicating Gram negative and septicaemia in consumption coagulopathy (DIC) was published by Lasch et al in 1967 [7]. Siegal et al [8] observed that out of 118 patients of DIC, 21 were due to Gram negative septicaemia. In our study, out of 23 patients of Gram negative infection 8 had septicaemia and 5 DIC. In Gram positive infection, out of 15 patients 7 had septicaemia and 4 DIC. While there was no significant difference between Gram positive and Gram negative infection in PT, PTTK, TT, and fibrinogen levels, the platelet count was reduced in 10 out of 23 Gram negative infections compared to only one out of 15 Gram positive infections (Table-1). In an extensive review, Yoshikawa et al cited multiple studies implicating Gram negative infection with low platelet count and DIC but few with Gram positive infection [9].

Coagulation abnormalities and Dengue fever

Thrombocytopenia is the most sensitive screening test for Dengue fever and was present in 27 out of 38 (71%) patients. Mechanism includes depression of megakaryocyte function, increased destruction of mature platelets and decreased platelet half-life [11]. A rebound increase in platelet count occurs during convalescence. Increase in PT, PTTK and TT were seen in 5 to 13% patients only. Interestingly 15.7% of these patients revealed subnormal PTTK levels suggesting procoagulant activity (Table-1). Compared to control

group, differences in parameters other than platelet count were not significant. These findings are at variance with those reported earlier where prolonged PT was found in 33.3% and prolonged PTTK in 54.6% [14], may be due to difference in natural history of Dengue fever in Indian subcontinent. None of our Dengue patients had hypofibrinogenemia or DIC. On the contrary 8 out of 38 patients of Dengue had fibrinogen levels >400mg/dl compared to 4 out of 58 non-Dengue patients. Haemoconcentration due to fluid shift might have been responsible for this hyperfibrinogenemia.

Acute infection, DIC and coagulation abnormalities

DIC has been reported in a variety of infections including septic abortion, viral infections like herpes, hepatitis, haemorrhagic fevers, septicemia, malaria and rickettsial infection. It was present in 14 of the 96 patients in this study; in 10 of them with coexistent septicaemia. Gram positive infection was present in 4, Gram negative in 5 and undefined infection in 5 (Table 3).

Concept of DII (Disseminated intra-vascular inflammation) has been proposed in lieu of DIC since the main feature of this pathologic condition is the damage to endothelial cells due to extensive systemic inflammation [15]. Lipo-polysaccharides, infectious organisms and immune complex mediated damage to endothelial cells alters its haemostatic properties such that the antithrombotic surface gets converted to a prothrombotic surface which expresses tissue factor and a prothrombin activator which can generate thrombin independent of intrinsic or extrinsic path [6]. This prothrombotic state and resultant thrombin is counteracted by concurrent or subsequent fibrinolytic activity with consumption coagulopathy and post depletion rebound and overshoot in the levels of coagulation factors. Depending upon the underlying disease and the time at which patient is evaluated, different laboratory results may be obtained.

We used FDP >25µg FEU/ml and D-dimer >1µg FEU/ml as diagnostic criteria for DIC as recommended by Yu et al, who found a combined highest sensitivity, specificity and efficiency of 91, 94 and 95% for these parameters [10]. Carr et al observed that FDP >20µgFEU/ml provided best sensitivity (100%) and D-dimer >1.0µgFEU/ml maximum specificity [16]. Fibrinogen levels at a cut-off of 150 mg/dl had poor sensitivity though good specificity like in our study. Positive predictive value of platelet counts <1.5 lac/mm³ was 66% in their study compared to 19.5% in ours. This increased to 47.3% on exclusion of Dengue

fever patients, though predictive value of other parameters was not significantly affected. We also observed that as a single parameter PTTK provides sensitivity of 78.6% and specificity of 81.7% for diagnosing DIC in acute infection. It was also observed that predictive value of negative test for routine parameters ranged between 88 to 95% (Table-4).

Most of the hospitals do not have facilities for analysis of FDPs and D-dimer. DIC being a medical emergency requiring energetic management needs to be detected early. Therefore we analysed our data to find combinations in routine coagulogram which will help clinicians at peripheral hospitals to detect DIC in a background of acute infection and septicaemia. We excluded Dengue fever patients as neither Dengue is routinely encountered nor did we find DIC in any of our Dengue patients. A combination of PTTK >38 sec and PT >15 sec could detect 11 out of 14 DIC patients with a false positivity of 3 in 44 non DIC patients giving a sensitivity of 78.6% and specificity of 93.2%. Similarly a combination of PTTK >38 sec with platelet count <1.5 lac/mm³ could detect 10 out of 14 patients of DIC giving sensitivity of 71.5% and specificity of 95.2%. Yu et al [10] observed a combined sensitivity of PT/PTTK + fibrinogen of 22% though the specificity reached 100%. In our study also, combinations with fibrinogen as one of the parameters gave very poor sensitivity.

We recommend that coagulation parameters should be assessed in all patients of acute severe infection for early detection of DIC. A combination of FDP >25µg FEU/ml & D-dimer >1µg FEU/ml is a sensitive and specific indicator of DIC. Out of the two, D-dimer is the investigation of choice. If facilities for FDP and D-dimer estimation are not available, a combination of PTTK and platelet count is reasonably sensitive and specific. Coagulograms done to evaluate bleeding disorders or as preoperative screen, may give false positive results due to acute infection and should be repeated after acute infection subsides. Values of PTTK less than normal range may be an indication of early procoagulant phase of deranged coagulation. These patients need to be monitored. How many of these will progress to DIC is a subject for further study.

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