Disseminated Intravascular Coagulation Findings in 100 Patients

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Abstract

A retrospective study of 100 patients with disseminated intravascular coagulation from 1993 to 1997 is reported. Forty-five patients were neonates with a mean age of 12.6 days and 55 patients were infants, children and adolescents with a mean age of 6 years and 3 months. Most of them (91.5%) had complicated underlying conditions which included congenital anomalies, prematurity, malignancy, hematological and various diseases. Additionally, every patient had triggering conditions commonly identified as gram-negative septicemia. Bleeding and thromboembolic manifestations were found in 59.4 per cent and 19.8 per cent, respectively. The laboratory findings revealed red blood cell fragmentation, 89.6 per cent and thrombocytopenia, 85.8 per cent. Natural anticoagulants were studied in a few cases and revealed low levels of antithrombin III and protein C. The prompt effective management included treatment of underlying diseases, identification and relief of triggering conditions, correction of thrombocytopenia and coagulopathy, and fully supportive care. The overall case-fatality rate was 41.6 per cent which was not correlated with age, underlying diseases, triggering conditions, manifestation of bleeding, thromboembolism or shock, and exchange transfusion. However, a significant lower case-fatality rate was found in patients with positive culture (25%) as compared to those with sepsis and negative culture (51.7%) ($p = 0.044$). In addition, the febrile neutropenic patients, who showed good response to the administrated granulocyte-colony stimulating factor (G-CSF), survived from the DIC.

Key word : DIC, Septicemia, Sepsis, Thromboembolism

Disseminated intravascular coagulation (DIC) is a serious complication found in critically-ill patients. From 1983 to 1987, the reported case-fatality rate among children with DIC at Ramathibodi Hospital was 52 per cent (1). Recently, medical care for the seriously ill patients has been markedly

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improved. There are various advanced technologies, such as mechanical ventilators, granulocyte colony-stimulating factor (G-CSF)[2], broad spectrum antimicrobial agents, and laboratory identification of causative microorganisms. The survival of very sick patients is significantly increased.

This paper presents the findings of DIC among 100 patients admitted to the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok from 1993 to 1997.

MATERIAL AND METHOD

Patient selection

The diagnostic criteria for DIC were based on clinical manifestations of the critically ill patients with certain conditions that could trigger DIC. They might have bleeding or thromboembolic episodes. The patients had at least 2 out of 3 criteria of the hematological findings which included: (1) thrombocytopenia (platelet count <100,000/μl), (2) red blood cell fragmentation, and (3) an abnormal coagulogram.

Patient population

One hundred patients who were qualified by the inclusion criteria were retrospectively studied. The management included specific treatment of underlying diseases, identification and relief of the triggering conditions, correction of thrombocytopenia and/or coagulopathy, and fully-supportive care. If the patients had bleeding or the potential for serious bleeding episodes, adequate replacement therapy, such as platelet concentrate, fresh frozen plasma (FFP) and cryoprecipitate was provided. Low molecular weight heparin (LMWH, Fraxiparine®) was given to patients with extensive or major vessel thrombosis. In cases of infection, appropriate antimicrobial agents were administered. Broad spectrum antibiotics for eradicating gram-positive and gram-negative bacteria were initially given and altered according to the identified microorganisms. The antifungal agent, amphotericin B was considered in cases of febrile neutropenic patients who did not respond to empirical antibiotics or when clinically indicated. Intravenous G-CSF of 5 μg/kg was given to the febrile neutropenic patients who had normal bone marrow reserves. Intravenous immunoglobulin was tried in a few cases of infection inducing hemophagocytic syndrome. Additionally, exchange transfusion was considered in patients with persistent triggered events who did not respond to all of the above mentioned management. Exchange transfusion was performed using FFP reconstituted packed red cell. Platelet concentrate was transfused after the exchange transfusion.

Laboratory method

The complete blood count and coagulogram were performed by standard hematological methods. The causative bacteria and fungus were determined by standard cultural technique. Fibrin degradation product (FDP) was measured by reverse hemagglutination test. The commercial antibody to fibrinogen was used. The anticoagulants of antithrombin III, protein C and protein S were determined by chromogenic peptide substrate technique.

Statistical methods

The significance of various factors on the outcome was calculated with chi-square test. The p value of less than 0.05 was considered to be statistically significant.

RESULTS

Forty-five patients were neonates with a mean age of 12.6 days (range 2-28 days) and 55 patients were infants, children and adolescents with a mean age of 6 years and 3 months (range 40 days to 17 years). The male to female ratio was 1.3:1. A total of 106 episodes of DIC were found among these 100 patients. Most of them (91.5%) had identified underlying conditions which included congenital anomalies, prematurity, malignancy, hematological diseases, and various diseases as shown in Table 1. Additionally, every patient had triggering condition identified as infection and one-third had more than one triggering condition (Table 2). The infection induced the clinical features of systemic inflammation such as fever or hypothermia, leucocytosis or leucopenia, tachycardia, tachypnea or respiratory failure. Septicemia and sepsis were defined for the patients with positive and negative hemoculture, respectively. The commonly identified causative microorganism was gram-negative rod (Table 3). Twelve out of 51 patients had more than one causative microorganism.

Sixty-three out of 106 episodes of DIC (59.4%) revealed bleeding episodes manifested at the skin (petechiae or ecchymosis), 35.5 per cent, gastrointestinal tract, 31.6 per cent, respiratory system, 23.7 per cent, central nervous system, 5.3 per cent, nose, 2.6 per cent and ear, 1.3 per cent. One-

Table 1. The underlying diseases found in 106 episodes of DIC.

Underlying diseases		Number
1.	Congenital anomalies (34%)	38
	congenital heart disease	20
	gastrointestinal anomalies	11
	Down's syndrome	3
	others : conjoint twin, chylothorax, bilateral choanal atresia, cell mediated immune response defect	4
2.	Prematurity (27.5%)	31
	<1,000 g	19
	1,000-1,500 g	2
	>1,500-2,000 g	6
	>2,000-2,500 g	4
3.	Malignancy (22%)	25
	acute leukemia	21
	others : lymphoma, myelodysplastic syndrome, malignant astrocytoma, osteosarcoma	4
4.	Hematological diseases (6%)	7
	acquired severe aplastic anemia	3
	others : autoimmune hemolytic anemia, cyclic neutropenia, G6PD deficiency, postsplenectomized ß thalassemia/HbE disease	4
5.	Miscellaneous (11%)	12

Table 2. The identified triggering conditions found in 106 episodes of DIC.

Triggering conditions		Number
1.	Infection (100%)	106
	septicemia	51
	sepsis	55
2.	Hypoxia-acidosis-ischemia (13%)	14
	respiratory distress syndrome	11
	meconium aspiration syndrome	2
	polycythemia	1
3.	Tissue injury and liberation of tissue factor (12%)	13
	necrotizing enterocolitis	12
	burn (60%)	1
4.	Other causes (26%)	27
	postoperation	23
	post exchange transfusion*	3
	Russell viper snake bite	1

* due to hyperbilirubinemia in the newborn

Table 3. The causative microorganisms found in 106 episodes of DIC.

Microorganisms		Number
1.	Gram-negative rod (69%)	54
	Pseudomonas aeruginosa	15
	Klebsiella pneumoniae	10
	Escherichia coli	9
	Enterobacter cloacae	5
	Non-typhoidal salmonella	3
	Salmonella typhi	2
	Other gram-negative rods*	7
	Unidentified gram-negative rods	3
2.	Gram-positive cocci (26%)	20
	Staphylococcus aureus	8
	Staphylococcus coagulase negative	3
	Streptococcus group	8
	Streptococcus enterococci	1
3.	Fungus (5%)	
	Candida albicans	4

**Pseudomonas fluorescens, Aeromonas hydrophila, Proteus mirabilis, Moraxella lacunata, Acinetobacter calcoaceticus anitartus, Citrobacter freundeii, Vibrio cholera*

third had more than one bleeding site. Moreover, 21 out of 106 episodes of DIC (19.8%) showed 26 thromboembolic manifestations which included necrotic skin, 38.4 per cent, ecthyma gangrenosum, 19.2 per cent, purpura fulminans, 11.5 per cent, gangrene of toe, 7.7 per cent, gangrene of colon, 7.7 per cent, and 3.8 per cent each for cerebral venous sinus thrombosis, thrombus at right atrium, thrombosis at anastomostic site of coarctation and catheter-related venous thrombosis. Simultaneously, 15 out of 106 episodes had both bleeding and thromboembolic manifestations. Additionally, the clinical finding of shock and threatened shock were found in 32 per cent and 7.5 per cent of the patients, respectively.

The laboratory findings revealed red blood cell fragmentation, 89.6 per cent and thrombocytopenia, 85.8 per cent. Abnormal coagulograms were found in 84 out of 85 patients. The rest of the patients did not have coagulogram testing due to technical difficulty in obtaining blood samples. The abnormal coagulogram included shortened activated partial thromboplastin time (APTT), 3.6 per cent, prolonged APTT, 91.7 per cent, prolonged prothrombin time, 91.7 per cent and prolonged thrombin time, 67.1 per cent. Thirty-eight out of 106 episodes of DIC patients had leucocytosis ranging from 10,000 to 49,000/μl. Twenty-four out of 106 episodes had a total white blood cell count less than 1,000/μl and all were acute leukemia patients receiving chemotherapy except three who had severe acquired aplastic anemia. FDP of higher than 40 μg/ml was found in 16 out of 20 patients. In addition, the natural anticoagulants were studied in five patients and revealed low levels of antithrombin III and protein C. Serial weekly specimens were determined in 2 patients and revealed that the increment of the anticoagulants was corresponded to the clinical improvement (Table 4).

Apart from antimicrobial agents and fully-supportive care, replacement therapy including packed red cells, 52.9 per cent, FFP, 82.8 per cent, platelet concentrate, 74.7 per cent and buffy coat, 2.3 per cent was given. Exchange transfusion was performed in 16 patients with unresponsive critically-ill manifestations. The overall case-fatality rate was 41.6 per cent (44/106). There was no correlation between case-fatality rate and age, underlying diseases, triggering conditions, manifestations of bleeding, thromboembolism or shock, and exchange transfusion. However, the patients with positive culture for microorganism had significantly lower case-fatality rate (4/16=25%) as compared to

Table 4. The anticoagulants of antithrombin III, protein C and protein S among five patients with DIC.

Underlying	Age		Anticoagulants* (%) Antithrombin III	Protein C	Protein S	Triggering conditions
Preterm 2100 g	4 d		25	33	26	Sepsis, urinary tract infection caused by E. coli
Full term 3500 g	28 d		24	32	53	Sepsis
Autoimmune hemolytic anemia	8 year		30	17	74	*Pseudomonas aeruginosa* septicemia
Acute leukemia	3 year, 6 m	D1	56	38	nd	
		D7	72	52	nd	*Pseudomonas aeruginosa* septicemia
Acute leukemia	4 year, 6 m	D1	39	26	96	*Staphylococcus aureus* septicemia
		D7	41	39	nd	
		D14	39	21	96	
		D21	87	77	116	

* Normal range 70-140 % , full term 20-50%; D = day after onset of DIC; nd = not done

those with sepsis and negative culture (15/29= 51.7%), (p = 0.044). Additionally, 15 out of 24 patients with febrile neutropenia (absolute neutrophil count < 1,000/μl), who were responsive to G-CSF administration, survived from the DIC while 6 patients with acute leukemia in relapse phase and 3 patients with severe acquired aplastic anemia succumbed to fulminant infections.

DISCUSSION

The case-fatality rate of patients with DIC in this study (41.6%) was not much lower than that of the previous study[1] (52%). The accompanying underlying diseases in this study were more complicated and required intensive care, especially very low birth weight, less than 1,000 gram. Although the patients were in the critical state of DIC, which manifested shock, extensive bleeding or thromboembolism, there was no correlation with the case-fatality rate as shown previously[1]. The effective medical management was able to stop the rapid ongoing process of DIC. Moreover, the case-fatality rate among patients with positive for microorganisms culture was significantly lower than those with negative culture. When the causative microorganisms were accurately identified, the appropriate antimicrobial agents were specifically used to eliminate them. The patients who received prompt and appropriate antibiotics had the lower mortality rate as compared to those who did not[3,4].

In this study, the success of any treatment may not be easily measured because this is an uncontrolled retrospective study. However, the administration of G-CSF to febrile neutropenic patients, who had adequate bone marrow reserve, revealed an excellent result. The adequate number of white blood cells was the major defensive barrier in eradicating causative bacteria or fungus.

Importantly, the diagnosis of DIC should be suspected in critically-ill patients with certain conditions that could trigger DIC and should be confirmed by laboratory tests. The laboratory results found in patients with DIC were not different from others studied[5-8]. Recently, the benefit of antithrombin III or protein C concentrate administration among patients with DIC[9,10] was reported but they have not yet been available in Thailand. Fresh frozen plasma in the dosage of 10 ml/kg twice a day can be alternatively given. The effectiveness of FFP has been shown in a neonate with purpura fulminans induced by severe acquired protein C deficiency[12]. When the process of DIC is under control, the levels of anticoagulants and the number of platelets will gradually return to the normal range. Therefore, accurate diagnosis and prompt effective management are essential for the critically-ill patients with DIC.

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ภาวะลิ่มเลือดอุดตันกระจายในกระแสเลือด ในผู้ป่วยเด็ก 100 ราย

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รายงานภาวะลิ่มเลือดอุดตันกระจายในกระแสเลือด (DIC) ในผู้ป่วยเด็กจำนวน 100 ราย ในระหว่างปี พ.ศ.2536 ถึง 2540 ผู้ป่วย 45 ราย เป็นทารกแรกเกิด อายุเฉลี่ย 12.6 วัน และ 55 ราย เป็นเด็กโต อายุเฉลี่ย 6 ปี 3 เดือน ผู้ป่วยส่วนใหญ่ (ร้อยละ 91.5) มีโรคหรือภาวะผิดปกติ ได้แก่ ภาวะปริกำเนิด เกิดก่อนกำหนด มะเร็ง โรคเลือด และอื่น ๆ ผู้ป่วยทุกรายมีตัวไกกระตุ้นให้เกิดภาวะDICที่พบบ่อยที่สุดคือภาวะติดเชื้อกรัมลบในกระแสเลือดผู้ป่วยมีอาการเลือดออกร้อยละ 59.4 และภาวะลิ่มเลือดอุดตันในหลอดเลือดร้อยละ 19.8 การตรวจทางห้องปฏิบัติการพบ fragmented red blood cell ร้อยละ 89.6 จำนวนเกร็ดเลือดต่ำร้อยละ 85.8 ได้วัดระดับปัจจัยต้านการแข็งตัวของเลือดในผู้ป่วยบางราย พบว่า antithrombin III และ protein C มีระดับต่ำกว่าปกติ ผู้ป่วยได้รับการรักษาที่มีประสิทธิภาพ ได้แก่ รักษาโรคที่เป็นอยู่ ขจัดตัวไกกระตุ้นภาวะ DIC ให้ส่วนประกอบของเลือดทดแทน รวมทั้งให้การรักษาประคับประคองที่เหมาะสม อัตราตายของผู้ป่วยเท่ากับร้อยละ 41.6 ซึ่งไม่เกี่ยวข้องกับอายุ โรคที่เป็นอยู่ อาการแสดงที่มีเลือดออก ลิ่มเลือดอุดตันในหลอดเลือด ช็อค หรือการถ่ายเปลี่ยนเลือด อย่างไรก็ตาม ผู้ป่วยที่ให้ผลบวกจากการเพาะเชื้อจะมีอัตราตาย (ร้อยละ25) ซึ่งต่ำกว่า ผู้ป่วยที่มีภาวะโรคติดเชื้อที่ให้ผลลบต่อการเพาะเชื้อ (ร้อยละ 51.7) ($p = 0.044$) และผู้ป่วยที่มีจำนวนเม็ดเลือดขาวต่ำ (<1,000/มคล.) ที่ตอบสนองดีต่อ granulocyte-colony stimulating factor จะรอดชีวิตจากภาวะ DIC

คำสำคัญ : ดีไอซี, ภาวะลิ่มเลือดอุดตัน, ภาวะติดเชื้อในกระแสเลือด

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