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Dipyridamole and Low Doses of Heparin as a New Successful Physiopathologic and Therapeutic Approach in 2 Cases of Disseminated Intravascular Coagulation

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ABSTRACT

Objective: We report 2 cases of disseminated intravascular coagulation (DIC) successfully treated with the combination of the platelet adhesiveness blocker dipyridamole and low doses of intravenous heparin.

Methods: The first patient was a 17-year-old boy with septic arthritis; the second patient was a 12-year-old boy with a liver abscess. Both had hemocultures positive for *Staphylococcus aureus*. The diagnosis of DIC was defined by clinical signs of septicemia with fever, tachypnea, peripheral vasoconstriction, and low platelet counts (67,000/mm^3 and 47,000/mm^3, respectively). The second patient also presented with acute ischemia of the fingers and toes. General care was provided in the intensive care unit, and high doses of antibiotics were provided continuously (metronidazole and oxacillin or ceftriaxone). A 5% glucose solution containing dipyridamole (Persantine; Istituto De Angeli/Boheringer Ingelheim, Reggello, Italy) was administered by continuous intravenous infusion (20 mg/24 hours). In addition, regular heparin (Liquemin; Roche, Indianapolis, IN, USA) was administered at a dosage of 250 µg/kg per hour or 25 IU/kg per hour (6 mg/kg per 24 hours). These heparin doses are not able to promote complete blood anticoagulation. Treatment with heparin and dipyridamole was maintained for 10 days in the first patient and for 18 days in the second.

Results: By 48 hours after treatment with dipyridamole and low-dose heparin, both patients recovered and presented with a good clinical condition and increased numbers of circulating platelets. Both patients were discharged in a safe clinical condition in the second month after hospital admission.

Conclusion: Successful clinical recovery of 2 young patients with DIC with an unfavorable clinical evolution and a prognosis for a lethal outcome was achieved with the combination of a continuous infusion of dipyridamole and low doses of heparin.

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INTRODUCTION

Disseminated intravascular coagulation, a disease mainly established as a complication of disseminated septic states, has been understood as a physiopathologic result of the effect of increased thrombin coagulation on the conversion of fibrinogen-fibrin complex in the last main phase of the blood-coagulation cascade. DIC promotes diffuse microvascular thrombosis and multiple organ failure. Nevertheless, the use of heparin to induce blood anticoagulation, which is based mainly on the specific antithrombin effect of this drug [Hoffmann 2000; Silla 2003], has been associated with very high mortality. It increases the hemorrhagic risk and worsens the likelihood of multiple organ failure. Such outcomes are quite different from the good results obtained with heparin use for other venous thrombosis conditions without a systemic sepsis phenomenon.

In seeking the best therapeutic results, we considered that the physiopathology of DIC disease was linked to the following pathways: (1) isolated hypercoagulability, (2) isolated platelet hyperactivity, and (3) associated hypercoagulability and platelet hyperactivity.

The importance of the role of platelets may be understood by considering the fact that the heparin usually used as the only drug for DIC reversal, when it is administered in high intravenous bolus doses of 4 mg/kg body weight to promote complete blood coagulation, blocks only 20% of platelet activity, as was proved by Best in 1938; however, the patient's hemorrhagic risk increases significantly.

Because previous research showed the high efficiency of dipyridamole in blocking the platelet adhesiveness induced by adrenaline and thrombin [Mills 1967; Gray 1968; Gomes 1976, 1977], we decided to use the combination of heparin and dipyridamole in 2 patients with high-risk DIC.

CASE REPORTS

The first patient was a 17-year-old boy with septic arthritis, and the second was a 12-year-old boy with a liver abscess. Both had hemocultures positive for *Staphylococcus aureus*. The diagnosis of DIC was defined by clinical signs of

septicemia with fever, tachypnea, peripheral vasoconstriction, and low platelet counts (67,000/mm^3 and 47,000/mm^3, respectively). The second patient also presented with acute ischemia of the fingers and toes. General care was provided in the intensive care unit, and high doses of antibiotics were provided continuously (metronidazole and oxacillin or ceftriaxone). A 5% glucose solution containing dipyridamole (Persantine; Istituto De Angeli/Boheringer Ingelheim, Reggello, Italy) was administered intravenously continuously (20 mg/24 hours). In addition, regular heparin (Liquemin; Roche, Indianapolis, IN, USA) was administered at a dosage of 250 µg/kg per hour or 25 IU/kg per hour (6 mg/kg per 24 hours). These heparin doses are not able to promote complete blood anticoagulation. By 48 hours after treatment with dipyridamole and low-dose heparin, both patients recovered and presented with a good clinical condition and increased numbers of circulating platelets. The liver abscess was subsequently drained, and the necrotic fingers were amputated. Treatment with heparin and dipyridamole was maintained for 10 days in the first patient and for 18 days in the second. Both patients were discharged in a safe clinical condition in the second month after hospital admission (Tables 1 and 2).

DISCUSSION

It is well known that bacterial toxins produce different adverse effects in the body, and it is possible that future experimental research will establish the pathology standard for each specific infection vector with respect to DIC, as we observed in these cases with sepsis caused by *S aureus*. Considering that the blockade of circulation flow and therefore the microthrombosis caused by the effect of direct or indirect platelet hyperactivity on the endothelial lesion are a powerful mechanism of protection against germs, it is possible to understand that during toxemia caused by infections that are transient and refractory to antibiotics, associated treatment with a platelet adhesiveness inhibitor may help decisively in ensuring a patient's survival.

CONCLUSION

The present approach with continuous dipyridamole administration (20 mg intravenously every 24 hours) combined with heparin infusion (6 mg/kg body weight every 24 hours) produced the successful clinical recovery of 2 young patients. These patients had an unfavorable clinical evolution and a prognosis for a lethal outcome. They had presented with

Table 1. Case 1*

	Day						
	1	2	3	4	5	6	7
Platelets, /mm^3	65,000	105,000	119,000	285,000	342,000	350,000	265,000
PTTa, s	60	60	45/32	52/32	48/32	50/32	40/32
PT, % of normal	51%	55%	65%	64%	49%	45%	90%
BT	X	X	1 min, 15 s	1 min	1 min, 10 s	1 min, 20 s	1 min, 10 s
WBC, /mm^3	14,000	9990	13,200	19,500	10,000	9710	10,400
Band neutrophils	21%	16%	16%	10%	13%	12%	13%
Creatinine, mg/dL	0.9	0.9	0.9	0.9	0.9	0.9	0.9

*PTTa indicates activated partial thromboplastin time; PT, prothrombin time; BT, bleeding time; WBC, white blood cells.

Table 2. Case 2*

	Day							
	1	2	3	4	5	6	7	8
Platelets, /mm^3	47,000	47,000	76,000	76,000	229,000	221,000	277,000	238,000
PTTa, s	X	X	X	42/32	38/32	39/32	X	29/32
PT	24%	64%	X	63%	63%	73%	X	100%
INR	6.25	3.98	1.3	1.51	1.51	1.3	X	1.0
WBC, /mm^3	22,400	23,000	16,900	17,900	12,900	11,500	8600	17,100
Band neutrophils	35%	33%	20%	30%	12%	24%	20%	22%
Creatinine, mg/dL	2.6	2.2	1.2	1.2	1.6	1.3	1.8	1.2

*PTTa indicates activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cells.

pneumonia and septic arthritis (the first case) and pyogenic necrotic skin lesions with a multiple disseminated abscess (the second case). Both patients had a marked reduction of blood platelets, although they were receiving antibiotic therapy in the intensive care unit.

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