



Tramadol and Disseminated Intravascular Coagulopathy: A Case Report

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Abstract

Disseminated intravascular coagulopathy (DIC) is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanisms. The aetiology of this syndrome is different. In some instances it results due to drug such as cocaine in this report we report a case of DIC due to tramadol which is very rare.

Key words: Disseminated intravascular coagulopathy (DIC), Tramadol, bleeding

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Introduction

Disseminated intravascular coagulation (DIC) is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanisms [1]. The underlying causes of DIC are vary but it can be due to infection such as (Gram-negative bacteria or virus or parasite rickettsia or fungi. Neoplasms as Adenocarcinomas. Obstetric complications placental abruption, retained dead fetus, second-trimester abortion, amniotic fluid embolism, others. Haematological disorders acute promyelocytic leukaemia, intravascular haemolysis, histiocytic medullary reticulosis Vascular disorders Kasabach–Merritt syndrome (giant haemangioma), aortic aneurysm. Tissue injury crush injuries, burns, hypothermia, head injury or drugs such as cocaine and others [2,3].

Case

Male patient 29 years present in the reception of Hospital with vertigo, hypovolemic shock, anemia, hypotension, bleeding tendency, ecchymosis. the patient fallen down and cut wound in the skull. In the emergency department complete blood count and coagulation profile was done. The results showed prolonged PT and PTT over 100 and low platelet and red blood cells count. The patient admitted to intensive care unit (ICU) blood pressure was 80/50 with plasma expander hemacell 500cc the blood pressure improved change to 110/70. In the ICU, D- dimer was done the result is 7,5 (normal value 0,5), all other analysis liver, kidney, protein and arterial blood gases are normal. In ICU the patient received 29 unit of fresh frozen plasma and 20 unit of packed blood in addition to 14 unit of creol precipitate. After two days the patient stabilized and discharged from ICU to internal medical department where he continued treatment for another four days then discharge with good general condition. According to patient history there is no complaint or trauma or any known cause of DIC. The patient was on Tramadol 2 gram /day. Final diagnosis was DIC. The patient advised to consult a hematologist. The hematologist confirm that the patient do not have any hematologic problems.

Table 1. Coagulation profile and CBC of the patient

Date	HGB	WBC	PLT	RBC	INR
22-3	6,2	12,6	141	3,55	-
	6,1	12,2	122	3,3	2,73
23-3	9,3	12	132	3,5	4,11
	8,9	12,8	132	3,2	
24-3	9,3	11,9	187	3,53	4,52
	8,3	11,2	196	3,5	
25-3	11	11,9	196	4,2	2,9
	11	11,2	227	4,3	
26-3	11	11	227	4,3	2,3

HGB: haemoglobin. **WBC:** white blood cells. **PLT:** platelets. **RBC:** red blood cells.

INR: international normalized ratio.

Discussion

In DIC, the processes of coagulation and fibrinolysis are dysregulated, and the result is widespread clotting with resultant bleeding. One critical mediator of DIC is the release of a transmembrane glycoprotein called tissue factor (TF). TF is present on the surface of many cell types and is not normally in contact with the general circulation, but is exposed to the circulation after vascular damage. TF is released in response to exposure to cytokines (particularly interleukin 1), tumor necrosis factor, and endotoxin [4]. This plays a major role in the development of DIC in septic conditions. TF is also abundant in tissues of the lungs, brain, and placenta. This helps to explain why DIC readily develops in patients with extensive trauma. Upon activation, TF binds with coagulation factors which then triggers the extrinsic pathway (via Factor VII) which subsequently triggers the intrinsic pathway (XII to XI to IX) to promote coagulation. A study of sepsis and DIC in animal models has shown that a highly-expressed receptor on the surface of hepatocytes, termed the Ashwell-Morell receptor, is responsible for thrombocytopenia in bacteremia and sepsis due to *Streptococcus* reference (SPN) and possibly other pathogens. The thrombocytopenia observed in SPN sepsis was not due to increased consumption of coagulation factors such as platelets, but instead was the result of this receptor's activity enabling hepatocytes to ingest and rapidly clear platelets from circulation [5]. The affected person is often acutely ill and shocked with widespread

hemorrhage (common bleeding sites are mouth, nose and venipuncture sites), extensive bruising, renal failure and gangrene [6,2].the diagnosis is based on sever hemorrhage with prolongation of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) commonly seen in DIC reflect the underlying disturbance in the coagulation cascade. Additionally, a markedly reduced level of fibrinogen level is characteristic of DIC. High levels of fibrin degradation products, including D-dimer, are found owing to the intense fibrinolytic activity stimulated by the presence of fibrin in the circulation[1-3,7,8]. DIC classified in two types acute and chronic, the main difference between the two types is that platelets in chronic type remain within the normal range. Of the rare causes acute DIC is heat stroke, snake bites and recreational drugs (eg, cocaine) due to endothelial damage and release of tissue factor. Tramadol is one of the recreational drugs. The rare causes of chronic DIC is retained dead fetus syndrome: At first the mother can compensate, and production and consumption of fibrinogen are temporarily in equilibrium. Over several weeks, decompensation with severe hypocoagulopathy occurs unless the uterus is evacuated [2]. The only effective treatment of DIC is the reversal of the underlying cause. Anticoagulants such as heparin are rarely given and are given only when thrombus formation is likely to lead to imminent death (such as in coronary artery thrombosis or cerebrovascular thrombosis). Platelets may be transfused if counts are less than $5,000-10,000/\text{mm}^3$ and massive hemorrhage is occurring, and fresh frozen plasma may be administered in an attempt to replenish coagulation factors and anti-thrombotic factors, although these are only temporary measures and may result in the increased development of thrombosis[1-3].

Tramadol

Tramadol is a centrally-acting atypical opioid analgesic with additional serotonin-norepinephrine reuptake-inhibiting effects used to treat moderate to moderately severe pain [9]. Tramadol is marketed as a racemic mixture of both R and S stereoisomers [10]. It is often combined with paracetamol as this is known to improve the efficacy of tramadol in relieving pain. Tramadol is used primarily to treat moderate-severe pain, both acute and chronic [11,12]. Tramadol is recommended for the management of pain in fibromyalgia by the European League Against Rheumatism [13]. Its analgesic effects take about one hour to come into effect and 2–4 hours to peak after oral administration with an immediate-release formulation. On a dose-by-dose basis tramadol has about one-tenth the potency of morphine [14]. Tramadol have a large number of side effects but the most dangerous are respiratory

depression, epileptic form convulsions, syncope, Stevens-Johnson syndrome, elevated liver enzymes, pulmonary oedema and embolism, myocardial ischaemia. Of the rare blood disorders haemoglobin decrease and low platelet count. Gastrointestinal side effects include melena, gastrointestinal bleeding has been reported with the use of tramadol. On May, 13, 2014: 5,544 people reported to have side effects when taking tramadol hydrochloride. Among them, 12 people (0.22%) have Disseminated Intravascular Coagulation. They amount to 0.02% of all the 67,897 people who have Disseminated Intravascular Coagulation. The data reveal 2,4, 6 patients in the years 2001, 2011 and 2012 respectively which mean increased number of cases. The incidence rate was 42,86% in less than one month after ingestion of tramadol and 57,14 from 1-6 months after ingestion of whom 71,43% were males and 14,29% aged 30-39 years and the remain are older [16]. Between January 2004 and October 2012, 5 individuals taking TRAMADOL reported DIC to the FDA. A total of 4526 TRAMADOL drug adverse event reaction reports were made with the FDA during this time period. [17]. Often the FDA only receives reports of the most critical and severe cases; these numbers may therefore under represent the complication rate of the medication.

The data obtained of our patient see Table 1 reveal low haemoglobin, low red blood cells count (RBC), elevated INR and moderate decrease of the platelet count, this was clear during treatment period but was more pronounced in the first four days. These data confirm DIC diagnosis. Also as mentioned above about tramadol side effects we find that tramadol is associated with low RBC and platelet count which is rare but dangerous side effects of the drug. The data obtained agree with these side effects of tramadol. The elevated INR reflects consumption of the coagulation factors without deterioration of liver function test which mean the case was acute so there was no changes in protein content and this need months to be affected. The patient was drowsy and fell down, one of the side effect of tramadol is drowsiness and confusion. Elevated the value of D-Dimer reflect pulmonary injury in addition to hypotension are of the dangerous side effect of tramadol. According to the haematologist there was no haematologic disorder and according to the patient recognition he was swallowed two grams of tramadol per day. The signs and symptoms of DIC starts acutely in the first month after ingestion of this high dose which is similar to data of other reports. So in conclusion this was very rare case of tramadol induced DIC.

Conclusion

DIC is extremely dangerous syndrome which may be fatal if not treated correctly it have different causes as mentioned above. A number of reports show that DIC is associated with tramadol use. Our case may be considered one of the rare cases due to the absence of any predisposing factors for DIC except ingestion of tramadol. Also the data from the patient including full blood count and coagulation profile and other parameters make strong suggestion that this case of DIC is associated with tramadol. So my recommendation is to re-write the pamphlet of tramadol and mention that tramadol may cause DIC since there is accumulation of the data about this. Also we recommend that all authorities and world health organization take this issue seriously.

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