The Administration of Low Molecular Weight Heparin In Severe Case of Covid-19, A Case Report

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ABSTRACT
Coagulopathy and disseminated intravascular coagulation (DIC) is one of the complications of the corona virus disease 2019 (Covid-19) that can lead to death. Several studies have shown that anticoagulants provide good clinical outcomes in Covid-19 patients, especially in severe cases. This case emphasizes the administration of low molecular weight heparin (LMWH) to prevent venous thromboembolism (VTE) in severe case of Covid-19.

Key Words: Covid-19, coagulopathy, thromboembolism; anticoagulant

Introduction
Case Fatality rate caused by Covid-19 are relatively high. In Indonesia, the case fatality rate caused by Covid -19 on May 8, 2020 reached 7.2% and 6.9% globally (1,2). The majority of severe cases of Covid-19 have met the criteria of the Third International Consensus Definitions for Sepsis (3). Endothelial dysfunction caused by sepsis can cause an increase in thrombin production which causes a hypercoagulable state in patients with infections including viruses (4). The International Society of Thrombosis and Haemostasis (ISTH) has introduced the term of sepsis-induced coagulopathy (SIC) (5,6). Prolonged bed rest also increases the risk of VTE in severe Covid-19 patients. Evidence shows that occlusion and micro-thrombosis occur in small pulmonary blood vessels on pathological examination (7).

Low molecular weight heparin is the most commonly used anticoagulant in hospitals to prevent both VTE and DIC. Studies show that LMWH therapy provides a better prognosis in patients with severe covid-19 who meet SIC criteria or with increased D-Dimer level (8). In this report, we describe our experience of giving LMWH to severe Covid-19 patient at Udayana University Hospital, Bali, Indonesia.

Case Report
In March 2020, a 65 years old male, came with complaint of fever since four days before admitted to the hospital, the fever was felt suddenly high. The patient also complained of dry cough and shortness of breath since three days before admitted to the hospital and felt getting worse. The patient did not complain of chest pain. The patient had no history of overseas travel in the past 14 days, but the area of residence of the patient included an area with local transmission of Covid-19. Patient had a history of hypertension and congestive heart failure due to coronary artery disease, routinely taking medication including clopidogrel 75 mg, amlodipine 5 mg, valsartan 80 mg, atorvastatin 20 mg, and bisoprolol 2.5 mg.

On physical examination, we found that the patient was fully alert; blood pressure of 130/80 mmHg; pulse of 110 beats per minute; respiration of 32 breaths per minute; body temperature of 37.6 °C; oxygen saturation of 88-90% in room air, 93% with nasal cannula of 6 liters per minute, 98% with simple face mask of 6 liters per minute.

On physical examination of the lung we obtained rhonchi in the right and left lung basal region. The chest radiograph examination showed evidence of pneumonia in the lower field of the lung (figure 1a). On laboratory examination we found lymphopenia (700 per μl); elevated of neutrophil...
Fig. 1. Chest radiographs showed progression of bilateral infiltrates of the lung, and improvements of chest radiographs on the follow-up. a: March 14 (hospital day 1 / illness day 5); b: March 18 (hospital day 4 / illness day 8); c: March 28 (hospital day 10 / illness day 14); d: May 5 (hospital day 17) / illness day 21).

Fig. 2. The thoracic computerized tomography scan of the patient. a: lung window, ground glass opacity in both lung fields; b: mediastinal window, hyperdens area on the right pulmonary artery branch (arrow).

to lymphocyte ratio (8.32); elevated of sedimentation rate (126 mm per hour); elevated of alanine aminotransferase (75 U/L) and aspartate aminotransferase (62 U/L); partial pressure of oxygen (PaO2) of 128 mmHg; and PaO2 / Fraction of inspired oxygen (FiO2) = 256. Examination of severe acute respiratory syndrome corona virus 2 (SARS-Cov-2) from nasopharyngeal swab specimen using the real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) method showed a positive result. The treatment that had been given was supportive therapy, including oxygen of 6 liters per minute through a simple face mask; normal saline 500 ml in 24 hours plus high dose vitamin C 1000 mg in 24 hours; antibiotic levofloxacin 750 mg every 24 hours intravenously; N-Acetylsistein 200 mg every 8 hours; paracetamol 500 mg every 8 hours; and routine medication taken before is continued.

On day 4 of hospitalization (illness day 8), the patient complained of worsening shortness of breath with respiration rate of 32 breaths per minute, and oxygen saturation of 95% with an oxygen of 6 liters per minute through a simple face mask. The second chest radiograph showing increase infiltrate of the lung (figure 1b). In computerized tomography (CT) scan showed the presence of ground-glass opacity (GGO) in both lung fields, especially in the region of subpleural (figure 2a), and hiperdens area on the right pulmonary artery branch as a marker of lung thromboemboli (figure 2b). Coagulation test results showed an activated partial thromboplastin time (APTT) of 29.3 seconds; prothrombin time (PT) of 9.3 seconds; international normalized ratio (INR) of 0.9; and an elevated of D-Dimer (1,514 ng/mL). The therapy added at that time was meropenem 1 gram every 8 hours intravenously; loxinapir/ritonavir 400/100 mg orally every 12 hours; chloroquine phosphate 500 mg every 12 hours; and enoxapharin 40 mg every 24 hours subcutaneously. On day 5 of hospitalization (illness day 9) the patient showed improvement of clinical condition, shortness of breath was decreasing, vital signs were stable, and oxygen saturation of 98-99%. Repeat chest radiographs were performed on hospitalization day 10 and 17 (illness day 14 and 21) showing reduction of lung infiltrates (Figure 1c and 1d). Examination of SARS-Cov-2 from nasopharyngeal swab specimens using rRT-PCR method showed a negative result on hospital day 22 and 24 (illness day 26 and 28). The patient was discharged from the hospital in good clinical condition.

Discussion

Until now there has been no specific therapy for Covid-19, the therapy regiment given is for supportive purposes and to prevent complications. We report this case with therapy of low molecular weight heparin as supportive therapy to prevent complications of VTE and death in severe cases of Covid-19. Based on WHO guidelines, our case met the criteria of severe Covid-19 (respiratory rate > 30 breaths per minute; severe respiratory distress; or peripheral capillary oxygen saturation (SpO2) ≤ 93% on room air). WHO guidelines recommend the administration of low molecular weight heparin to reduce the incidence of VTE in adolescent and adult patients if there are no contraindications in severe cases of Covid-19 (9).

Padua score can be used as a risk assessment model to identify patients at risk for VTE. High risk of VTE was defined as a cumulative score of at least four (10). Our patient in this case had a cumulative score of four
because of decreased mobility and heart failure. Tang et al. used SIC score ≥4 and D-Dimer >6 upper limit of normal as an indication of anticoagulant therapy, the results showed that therapy with LMWH was associated with a better prognosis in severe cases of Covid-19 (8).

Evidence of abnormal coagulation parameters in our case is proven by the increase of D-Dimer. Report from hospitals in China found that there was a 36% increase in D-Dimer and a minimal increase of APTT and PT in Covid-19 patients (11). Reports from Wuhan hospital found that an increase of D-Dimer of more than 1000 ng mL at hospital admission was associated with increased mortality (OR of 18.42, 2.64-128.55, p = 0.003) (12). In patients who are already confirmed and are also still suspected to be infected with Covid-19, coagulation tests should be performed at the time of hospital admission, including platelet count, PT, APTT, D-dimer, and fibrinogen. Increase of D-Dimer can be seen within 7-11 days after the onset of symptoms or 4-10 days of hospitalization (8,12,13). In SARS-Cov-2 infection, the abnormal finding of the coagulation test is mild and with no clinical bleeding found. The occurrence of coagulation test abnormalities is related to the inflammatory response that occurs due to infection (14). Viral infection will initiate systemic inflammation that will cause activation of coagulation and thrombin formation, this phenomenon is known as thromboinflammation or immunothrombocytosis (15,16).

For hospitalized patients, especially those who are in critical condition, the use of LMWH or unfractionated heparin (UFH) is recommended over direct oral anticoagulants because it has a short half-life and can be given parenterally (14). The use of prophylactic VTE can also enhance the experience of doctors caring for Covid-19 patients, this is because the routine use of VTE prophylaxis in the Asian populations is low (17). There is evidence that shows incidences of microvascular thrombosis and pulmonary embolism in patients with Covid-19. Microvascular thrombosis may be responsible for the occurrence of multiorgan failure in Covid-19 patients (18,19). However, based on current data, the use of anticoagulants in therapeutic doses has not been recommended except for indications such as new or recent diagnosis of VTE (14)

In our case, we cannot claim that the improvement in the clinical condition of patient is solely due to the administration of LMWH, because the supportive and antiviral therapy that was given also has a role. Anticoagulant, especially LMWH, can prevent deterioration and complications including mortality in severe cases of Covid-19 who has a high risk of VTE.

References


