Mutiara Medika: Jurnal Kedokteran dan Kesehatan

http://journal.umy.ac.id/index.php/mm

Vol xx No x Page xx-xx January/July Year

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| **Anticoagulant Therapy in Moderate to Severe COVID-19 Patients** *Terapi Antikoagulan pada Pasien COVID-19 Sedang sampai Berat* **Agus Fitriyanto Achmad 1\*, Yuni Iswati Raharjani2, Zidni Setyaningrum, Bagus Andi Pramono3, Dita Ria Selvyana5, Sri Pramesthi Wisnu Bowo Negoro6**1Haematologist and Medical Oncologist, Internal Medicine Department of Panembahan Senopati Hospital2Pulmonologist, Internal Medicine Department of Panembahan Senopati Hospital3Internist, Internal Medicine Department of Panembahan Senopati Hospital4Cardiologist, Internal Medicine Department of Panembahan Senopati Hospital5Internist, Internal Medicine Department of Medical Faculty of Muhammadiyah Yogyakarta University6General Practitioner |
| **DATA OF ARTICLE:**Received: …Reviewed: …Revised: …Accepted: ...**\*CORRESPONDENCE:** agusfachmad@yahoo.com**DOI:**…......**TYPE OF ARTICLE:**Case Report | ***Abstract*:** *Coronavirus disease-19 (COVID-19) has a spectrum of severity from no symptoms to serious complications. Coagulopathy is a serious complication of COVID-19 and that condition is a marker of poor prognosis. Anticoagulant drugs are often used as prophylaxis and thrombosis therapy in the treatment of COVID-19 patients. Anticoagulant therapy is indicated for moderate-severe COVID-19 patients. Low molecular weight heparin (LMWH) and Unfractionated Heparin (UFH) are anticoagulant drugs of choice for prophylaxis and thrombosis therapy in COVID-19 patients. Monitoring of bleeding, renal function, and platelet count needs to be done when administering anticoagulant drugs even if only as thromboprophylaxis. LMWH and UFH have good clinical efficacy with minimal side effects in the management of COVID-19 patients.****Keywords:*** *COVID-19; Coagulopathy; Anticoagulant; Low-Molecular-Weight Heparin; Unfractionated Heparin****Abstrak:*** *Penyakit COVID-19 memiliki spektrum derajat keparahan mulai dari tanpa gejala sampai dengan berbagai komplikasi berat. Koagulopati merupakan suatu bentuk komplikasi berat dari COVID-19. Koagulopati ini merupakan suatu penanda prognosis buruk pada pasien COVID-19. Obat antikoagulan sebagai profilaksis dan terapi trombosis banyak digunakan pada perawatan pasien COVID-19. Terapi antikoagulan diindikasikan untuk pasien COVID-19 derajat sedang-berat. Heparin Berberat Molekul Rendah (LMWH) dan Heparin tak Terfraksinasi (UFH) merupakan pilihan obat antikoagulan sebagai profilaksis maupun terapi trombosis pada pasien COVID-19. Monitoring perdarahan, fungsi ginjal dan jumlah trombosit perlu dilakukan saat pemberian obat antikoagulan meskipun hanya sebagai tromboprofilaksis. LMWH dan UFH memiliki efikasi klinis yang baik dengan efek samping minimal pada tatalaksana pasien COVID-19.****Kata Kunci :*** *COVID-19; Koagulopati; Antikoagulan; Heparin Berberat Molekul Rendah; Heparin tak Terfraksinasi* |

**INTRODUCTION**

COVID-19 (coronavirus disease 19) is caused by the new coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Currently, COVID-19 is a worldwide pandemic that emerged at the end of 2019(1). The disease has a spectrum of severity from no symptoms, mild, moderate, severe with multi-organ failure conditions, and until death (2,3).

Coagulopathy is a form of thromboembolism of the veins or arteries and this is a serious complication of COVID-19. This coagulopathy is a marker of poor prognosis in COVID-19 patients(4,5). There have been many reports regarding the incidence of thrombosis in COVID-19, the use of anticoagulant drugs as prophylaxis and thrombosis therapy, and the pathophysiology of thrombosis in COVID-19(6,7).

In this case report, we report a case series of administering anticoagulant therapy in moderate to severe COVID-19 patients with different comorbidities including diabetes mellitus, hypertension, coronary heart disease, chronic heart failure, diabetic ketoacidosis, acute kidney injury, and chronic kidney disease. This report can be considered in administering anticoagulants to COVID-19 patients in terms of indications, dosage, side effects, and clinical efficacy in the clinical setting of treatment for COVID-19 patients.

**CASE 1**

Mrs. A, 62 years old, with complaints of cough, shortness of breath, and fever for 5 days. Comorbidities hypertension, diabetes mellitus, and coronary heart disease. The patient was confirmed COVID-19 from a positive RT-PCR nasopharyngeal swab with chest X-ray bronchopneumonia. Mrs. A had moderate clinical symptoms with the d-dimer result was 1.08 µg/dl, 3.6 times normal value (0.3 µg/dl ). The patient has given enoxaparin (low molecular weight heparin / LMWH) 0.4 ml per 24 hours with a d-dimer evaluation result of 0.91 µg/dl (day 3 of LMWH), 0.63 µg/dl (day 4 of LMWH), 0.61 µg/dl (day of 6 LMWH), 0.38 µg/dl (day 9 of LMWH), then stop LMWH therapy. There was no bleeding during LMWH administration even in combination with aspilet. The patient went home with clinical and radiological improvement and a negative swab evaluation.

**Table 1**. Case-1 d-dimer progression after used enoxaparin

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| --- | --- |
|  | **Day Used Enoxaparin** |
|  | **Day-1** | **Day-3** | **Day-4** | **Day-6** | **Day-9** |
| **D-dimer (****µg/dl)** | 1.08 | 0.91 | 0.63 | 0.61 | 0.38 |
| **Dosage** | 0.4ml/24h | 0.4ml/24h | 0.4ml/24h | 0.4ml/24h | Stop |

**CASE 2**

 Mr. B, 35 years, complained of shortness of breath for 3 days preceded by cough and fever. There is no previous history of other diseases. Mr. B confirmed COVID-19 from positive RT-PCR nasopharyngeal swab with chest X-ray bilateral pneumonia especially right. The clinical symptoms were moderate severity with a d-dimer result of 1.29 µg/dl (4.3 times the normal value). The patient has given enoxaparin 0.4 ml per 24 hours. The evaluation result of d-dimer 2.16 µg/dl (day 3 of LMWH) then the dose was increased to 0.4 ml per 12 hours. The evaluation result of d-dimer 0.86 µg/dl (day 5 of LMWH) then reduces the dose to 0.4 ml per 24 hours. Evaluation result d-dimer on day 7 LMWH 0.3 µg/dl then stop. The clinical and radiological evaluation results improved.

**Table 2**. Case-2 d-dimer progression after used enoxaparin

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|  | **Day Used Enoxaparin** |
|  | **Day-1** | **Day-3** | **Day-5** | **Day-7** |
| **D-dimer (****µg/dl)** | 1.29 | 2.16 | 0.86 | 0.3 |
| **Dosage** | 0.4ml/24h | 0.4ml/12h | 0.4ml/24h | Stop |

**CASE 3**

Mr. D, 45 years old, complained of shortness of breath and cough for 3 days. Comorbidities hypertension and diabetic ketoacidosis. The diagnosis of COVID-19 was confirmed by a positive RT-PCR nasopharyngeal swab with chest X-ray bronchopneumonia. The patient had severe clinical symptoms with a d-dimer result > 4.00 µg/dl (>13.3 times the normal value). The patient has given enoxaparin 0.4 ml per 24 hours. The evaluation result of d dimer 3.36 µg/dl (day 2 of LMWH) then the dose was increased to 0.4 ml per 12 hours. The evaluation result of d dimer 2.48 µg/dl (day 10 LMWH) then the dose was decreased to 0.4 ml per 24 hours. The patient was clinically improving and can be active mobilization. The evaluation result of d dimer 1.78 µg/dl (day 13 LMWH) then enoxaparin stop.

**Table 3**. Case-3 d-dimer progression after used enoxaparin

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|  | **Day Used Enoxaparin** |
|  | **Day-1** | **Day-2** | **Day-10** | **Day-13** |
| **D-dimer (****µg/dl)** | > 4.00 | 3.36 | 2.48 | 1.78 |
| **Dosage** | 0.4ml/24h | 0.4ml/12h | 0.4mi/24h | Stop |

**CASE 4**

Mr. E, 77 years old, complained of shortness of breath for 1 day. Comorbidities chronic heart failure NYHA 3, hyperglycemia, acute kidney injury. The diagnosis of COVID-19 was confirmed by a positive RT-PCR nasopharyngeal swab with chest X-ray pulmonary edema mixed pneumonia and cardiomegaly. Creatinine serum was 2.61 mg/dL then improved to 1.64 mg/dL. The patient had severe clinical symptoms with a d-dimer result > 4.00 µg/dl (> 13.3 times the normal value). The patient has given enoxaparin 0.6 ml per 24 hours. The evaluation result of d dimer still > 4.00 µg/dl (day 5 of LMWH), enoxaparin was given with the same dose. The evaluation result of d-dimer 2.89 µg/dl (day 10 LMWH) and the dose of enoxaparin 0.4 ml per 12 hours. Then last evaluation result of d-dimer 1.76 µg/dl (day 12 LMWH). The clinical and radiological evaluation results improved, there was no bleeding during the administration of LMWH. The patient went home with clinical improvement.

**Table 4**. Case-4 d-dimer progression after used enoxaparin

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|  | **Day Used Enoxaparin** |
|  | **Day-1** | **Day-5** | **Day-10** | **Day-12** |
| **D-dimer (µg/dl)** | > 4.00 | > 4.00 | 2.89 | 1.76 |
| **Dosage** | 0.6 ml/24h | 0.6ml/24h | 0.4ml/12h | Stop |

**CASE 5**

Mrs. F, 60 years old, complained of shortness of breath and cough. Comorbidities chronic kidney disease stage V, anemia, hypertension, and diabetes mellitus. The diagnosis of COVID-19 was confirmed by a positive RT-PCR nasopharyngeal swab with chest X-ray pulmonary edema mixed pneumonia and cardiomegaly. The patient had moderate clinical symptoms with a d-dimer result of 1.39 µg/dl (4.6 times the normal value). The patient has given unfractionated heparin (UFH) 5000 IU per 12 hours. The evaluation result of d-dimer 1.34 µg/dl (day 4 of UFH), then UFH gave with the same dose. Then last evaluation result of d-dimer 0.97 µg/dl (day 6 UFH). The clinical and radiological evaluation results improved, there was no bleeding during the administration of UFH. The patient went home with clinical improvement.

**Table 5**. Case-5 d-dimer progression after used enoxaparin

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|  | **Day Used Unfractionated Heparin (UFH) Subcutaneously** |
|  | **Day-1** | **Day-4** | **Day-6** |
| **D-dimer (µg/dl)** | 1.39 | 1.34 | 0.97 |
| **Dosage** | 5000 IU/12h | 5000 IU/12h | stop |

**DISCUSSION**

Coagulopathy is a term that refers to any homeostasis problem that results in excessive bleeding or clotting and is commonly known as clot formation problem(8). The International Society of Thrombosis and Haemostasis (ISTH) has established and validated a sepsis-induced coagulopathy (SIC) score in addition to diagnostic criteria for overt DIC. (9–11). Chinese COVID-19 outbreak reports already used both ISTH definitions(12,13).

 Coagulopathy is common in SARS-CoV-2 infection and is marked by an increase of d-dimer (14). Guan et al report their large studies with 560 cases, 260 cases have increased d-dimer (46.4%). Their studies found that conditions happened 60% in ICU patients and 43% in nonsevere patients (5). Increased D-dimer levels are possibly due to inflammation caused by COVID-19 and subsequent activation of coagulation, as elevated levels have been related to several conditions other than thromboembolism, with infection being the main cause(15–17).

 In these cases, we found all of the patients have high d-dimer above the normal levels. Zhou et al(4) found that poor prognosis and increased mortality were related to elevated d-dimer. Zhang et al(18) examined 343 cases and found that d-dimer levels of over 2.0 mg/L could predict mortality with a sensitivity of 92.3% and a specificity of 83.3%. As a consequence, based on the disease's progression, maximizing a particular treatment may be the best choice(19,20). In mild to serious COVID-19 patients, interim advice from the International Society on Thrombosis and Haemostasis (ISTH) suggests prophylactic low-molecular-weight heparin (LMWH)(21,22).

 Low-molecular-weight heparins (LMWHs) are a new class of anticoagulants made from unfractionated heparin (UFH) and depolymerized chemically or enzymatically to yield fragments around one-third the size of heparin(23). They have some benefits over UFH, which has led to increased use for a range of thromboembolic indications(24). (24). LMWHs, activate antithrombin (AT) like UFH to create their key anticoagulant effect(23). Anticoagulants are low-molecular-weight heparins (LMWHs), such as dalteparin and enoxaparin. These medications are used to prevent venous thromboembolic disease (VTE) during an acute or elective hospital stay, to treat deep vein thromboses (DVT), pulmonary embolism (PE), and unstable angina, and are now prescribed in mild to serious COVID-19 with symptoms of coagulopathy(22,23,25). We used enoxaparin with prophylaxis dose to treated our patients in this case report and unfractionated heparin used in one case.

 If there is no contraindication such as platelet less than 25 x 109/L, ISTH suggested giving a prophylactic dosage of LMWH to all COVID-19 who needed to hospitalize(26). In another systematic review and meta-analysis showed that LMWH as safe as UFH. As a result, their efficacy is also debatable, owing to the possibility of bioaccumulation in patients with renal problems(27). Our Case-5 showed the use of unfractionated heparin (UFH) in chronic kidney disease patients, then gave good results from d-dimer level response became normal level without any complication happened.

Ning Tang et al. recently investigated the advantage of LMWH use in sepsis-induced coagulopathy and discovered that LMWH tends to be correlated with an improved prognosis in terms of mortality (40.0% vs 64.2%, p=0.029). Those with D-dimer >6-fold of the upper limit of average had a comparable gain (32.8 % vs 52.4%, P =.017)(13).

Since the evidence indicates that genetic risk factors and VTE prevalence differ significantly among ethnic groups, and since the incidence of VTE in Asian populations is low(28,29), a higher dose of LMWH may be recommended in non-Asian population with severe COVID-19. On the other hand, anticoagulant treatment for sepsis-associated DIC is still debatable(30,31). The ISTH created the SIC guidelines to direct anticoagulant therapy because platelet counts decrease and prothrombin time prolongation is connected to increased mortality, and hypofibrinogenemia is rare in sepsis. The utility of this simple score has already been shown (32).

 The three most serious drug-related complications associated with heparin and LMWH treatment are thrombocytopenia, bleeding, and osteopenia(33). Heparin-induced thrombocytopenia (HIT) affects 3 to 5% of patients who administer unfractionated heparin intravenously, compared to 0.5 percent of patients that receive subcutaneous LMWH, catheter flushes, or even small levels of heparin that leach from coated catheters. Heparin-induced Thrombocytopenia with Thrombosis (HITT) is a severe prothrombotic diathesis that can result in venous or arterial thromboembolism in 50% of cases. Under timely and successful care, approximately 20% of patients will have their limbs amputated, up to 30% will die, and survivors will have residual deficits that can lead to myocardial infarctions, strokes, and pulmonary emboli. Heparin should be stopped as soon as platelet counts drop dramatically (usually 50% of baseline), and lepirudin or argatroban (direct thrombin inhibitors) should be started if anticoagulation is needed(34,35). Five patients in this report had normal thrombocyte levels before and after used enoxaparin and UFH.

 Bleeding is the most common side effect of anticoagulant therapy and LMWH has a lower risk than UFH. Since LMWH is completely excreted by the kidneys, renal activity and creatinine clearance (CrCl), rather than only serum creatinine, should be controlled in elderly and frail patients. For patients in this indication group, the lowest CrCl ratio likely varies for various LMWHs, although a reasonable threshold is likely to be 30 mL/min. Lower than that can cause hemorrhaging and should not be used(33). Intermittent intravenous (IV) heparin causes more major bleeding than continuous IV heparin; however, continuous IV heparin and subcutaneous heparin cause almost the same amount of bleeding(33). In this report, all of the patient’s hemoglobin was still at the same level after used enoxaparin or UFH and there weren’t any symptoms associated with bleeding. Protamine can be used to counteract the effects of heparin if bleeding happens during UFH treatment. Protamine, on the other hand, tends to neutralize just about 60% of LMWH's anti-factor Xa activity(33). In Case-4, we calculated the CrCI (Cockcroft-Gault Equation)of the patient was approximately 20 mL/min, closed observation to this patient found no complication such as bleeding.

 Osteopenia and osteoporosis associated with heparin are linked to long-term treatment (usually more than one month). They are uncommon but often occur during breastfeeding and the postpartum phase, where they can lead to fractures spontaneously. In this report, all of the cases were only short-term therapy, so this complication didn’t happen. Balance disruption of osteoclasts and osteoblasts, abnormal collagen activation, and vitamin D synthesis disruptions can all induce heparin-associated osteopenia. (33).

**CONCLUSION**

 Anticoagulant has been widely recommended to be given to COVID-19 patients especially with moderate to severe degrees to reduce mortality from coagulopathy. In this report, either patient who used enoxaparin LMWH or heparin UFH gave a good response, all d-dimer levels gradually became normal and experienced clinical improvement without any complication happened.

**CONFLICT OF INTEREST**

There are no conflicts of interest declared by either of the contributors.

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