Heparin Resistance In A COVID-19 Patient: A Rare Occurrence

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Abstract: Coronavirus disease-2019 (COVID-19) in severe cases is associated with marked inflammation in mainly the lungs. Reports suggest a beneficial role of heparin/low molecular weight heparin (LMWH) in reducing mortality and morbidity in such patients.We have summarized potential beneficial, anti-inflammatory mechanisms underlying treatment of COVID-19 patients with heparin/LMWH. Herein, we present a rare case of severe COVID-19 showing Heparin Resistance (HR), which was primarily suspected due to constantly elevated inflammatory markers like CRP, D-dimer, IL-6 and subtherapeutic levels of aPTT when the patient was on Heparin. These parameters showed remarkable changes when Heparin was replaced by LMWH, Dalteparin and eventually the condition of patient ameliorated.[Parikh K Natl J Integr Res Med, 2020; 11(6):66-68]

Key Words: Heparin Resistance (HR), COVID-19, Coagulopathy, Heparin, Low Molecular Weight Heparin (LMWH), Dalteparin.

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Introduction: In March2020, global healthcare system was overwhelmed by the outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is the cause of the coronavirus pandemic (Covid-2019). The clinical manifestations of SARS-CoV-2 infection range from asymptomatic to severe pneumonia with acute respiratory distress syndrome, septic shock, and multi-organ failure. Important mechanisms underlying deterioration of disease is the cytokine storm. This phase is accompanied by high level of inflammatory markers, such as D-dimer, C-Reactive Protein (CRP), Serum Ferritin and IL-6.Even if the risk-benefit ratio has not been established, it has been recommended to give thrombo-prophylaxis with either UFH/LMWH.[1]

LMWH, such as enoxaparin, dalteparin and tinzaparin, are prepared via controlled chemical or enzymatic cleavage of Unfractioned Heparin (UFH) in a depolymerization reaction. They have more predictable action than UFH. The result is a better adverse reaction profile than the UFH, less requirements for monitoring, higher bioavailability, more predictable anticoagulant effect, resistance to inhibition by activated platelets and a lower incidence of heparin-induced thrombocytopenia. Other drugs approved as thrombo-prophylactic agents in critically ill patients include Betrixaban and Rivaroxaban.[2] Here in, we present a case report where the patient showed suspected Heparin Resistance (HR).

Case Details: A 73 year old male patient with complains of fever and cough since one week, was admitted to a tertiary care hospital. The patient tested positive for COVID-19 by Rapid Antigen Testing and RTPCR test. He was a known case of Hypertension and Chronic kidney disease.

On admission the patient was conscious and oriented. Temperature was 97.2°C, BP-126/86 mmHg, RR-18/min, pulse-72/min and was maintaining 98% Spo2 on room air. CT scan findings showed CO-RADS (COVID-19 Reporting and Data System) score 5. Initial laboratory findings within normal limits included PT:14.1sec(12.0-16.0),INR:1.01(0.8-1.2), apTT: 31. 9sec(20-35), raised inflammatory markers like D-dimer:1.01µg/ml(<0.5), Ferritin:125.2ng/ml(10-282), LDH:261U/L(100-250), CRP:133.39mg/L (<5.0) and IL-6:95.6pg/ml(0-4.4).

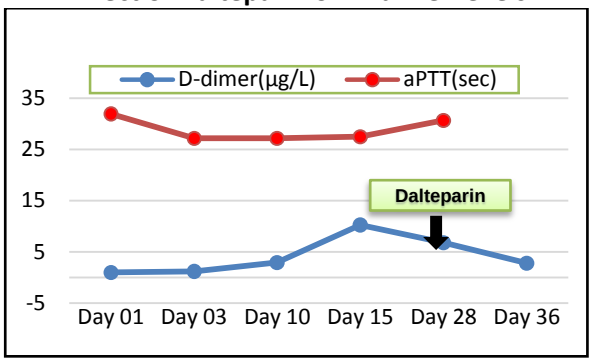
He was given Inj. Methylprednisolone 40mg for 10 days, Tab. Azithromycin 500mg for 5 days, Inj. Meropenem 1gm and Inj. Clindamycin 600mg I.V. thrice a day for 16 days. Inj. Heparin I.V. at 1000/hour (25,000U/50 ml) for 30 days. Other drugs given to the patient included Tab. Metoprolol 25mg, Tab. Clindipine 10mg, Tab. Teneligliptin 20mg, Tab. Sodium Bicarbonate 500mg, Tab. Prednisolone 10mg, Tab. Ecosprin, MDI Salbutamol and Ipratropium, MDI Budesonide. Patient was initially stable, later he became hypoxic and tachypneic and was put on 2L O2. Still he was unable to maintain normal SPO_2 and was put on Non-Re-Breather Mask (NRBM)12 L/min on 11th day of admission. On 12^{th}day Inj.

Remdesivir 100mg was started for 5 days. In the course of admission his condition deteriorated

and was further put on High Flow Nasal Canula (HFNC) with intermittent Bilevel Positive Airway Pressure (BIPAP) support. On 26thday patient was put on 2L O2 and was tested negative for COVID on 27thday. After starting Inj. Heparin I.V. at 1000U per hour, the usual protocol with aPTT monitoring, after heparin infusion, was initiated.

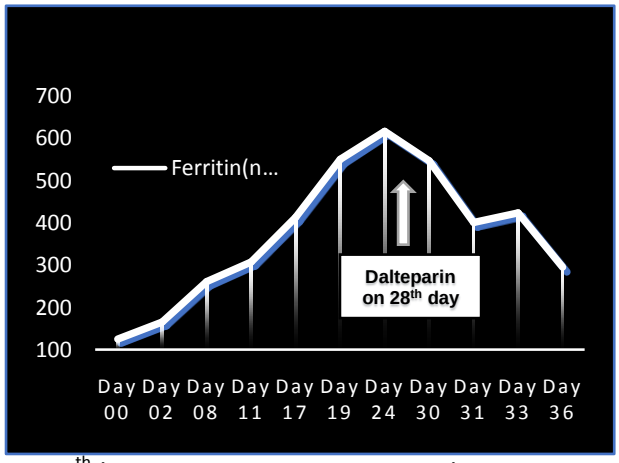
During that period it was difficult to achieve a therapeutic range for anticoagulation based on aPTT. Usually after giving Heparin the apTT rises twice the control value, which was not the same with this case. At all points of time it remained subtherapeutic. Neither there was any decrease in the D-dimer(Figure:1)

Figure: 1 Constant Sub-Therapeutic aPTT and Effect of Dalteparin on D-dimer levels



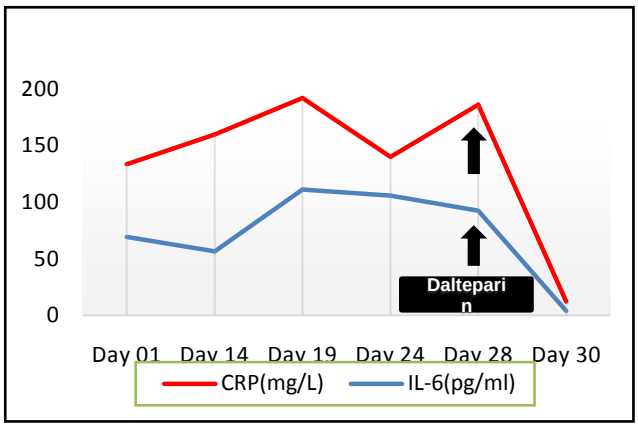
S.Ferritin levels further increased, measuring 616.8ng/ml on 24thday(Figure:2)The levels of inflammatory markers like D-dimer, CRP and IL-6 also remained elevated throughout these days when the patient was on Heparin(Figure:3).
Hence, HR was suspected.

Figure: 2 Effect of Daltepatin on Ferritin



On 28thday, CRP was 186. On same day, Heparin was stopped and replaced by Inj. Dalteparin 2500IU subcutaneously for 7 days. Along with that Tab. Warfarin 2mg for 3 days, Inj. Sulbactam sodium and Cefoperazone sodium 1.5mg for 5 days, Tab. Cefixime 200mg for 3 days were also given.Subsequently the condition improved after replacement of Heparin with Dalteparin. Also the laboratory parameters started to normalize (S.Ferritin:295ng/ml, LDH:253U/L, CRP:4.22mg/L, IL-6:4.0pg/ml). Finally on 36thday, patient was discharged.

Figure: 3 Decrease In Inflammatory Markers After Replacement Of Heparin With Dalteparin



Discussion: Importantnon-anticoagulant/anti-inflammatory property of heparin/LMWH specially focuses on: Inhibition of Heparanase(HPSE) activity, neutralization of cytokines, extracellular cytotoxic histones in the circulation by binding to the vast majority of chemokines/cytokinesand inhibit their synthesis including TNF-a, IL-6, and IL-8 via inhibition of NF-kB signalling.[3]

HR, a rare phenomenon, canbe defined as high doses of UFH, greater than 35,000 IU/day, required to raise aPTT to within therapeutically desired ranges. In this case we have given UFH dose upto 25,000IU/day for about a month with constant aPTT monitoring, stillit's level remained sub-therapeutic. Also there was no beneficial effect on the inflammatory markers.We ruled out other causes of thrombocytopenia, namely heparin-induced thrombocytopenia and disseminated intravascular coagulation.

Our primary suspicion, although rare was HR, it can result from a number of factors like increased heparin-binding protein levels (acute phase reactants), low ATIII levels (most common), increased heparin clearance levels and high Factor-VIII(f-VIII) levels.In context with the mentioned case, we contemplated the hypothesis of increased heparin-binding proteins due to COVID-19 as the mechanism for HR. Due to patient's pro-inflammatory state, causing a

non–antithrombin-mediated sequestration of heparin through increased heparin-binding proteins, as seen in patients with severe sepsis, where activated neutrophils release various heparin-binding proteins, resulting in HR. In this case COVID-19 led to the release of heparin-binding proteins (Eg. Interleukins), causing a decrease in bioavailability of heparin.[4]

Diagnosis of HR in different cases can be done via different parameters. We suspected our case to be HR based on the constantly low aPTT and raised inflammatory markers while on Heparin therapy for a long time. Although we were not able to obtain anti-Xa and f-VIII levels due to the costly nature of such tests, but a strong impression of a pro-inflammatory state, lead to the possibility of HR. A study documented about the resistance of UFHin SARS-CoV-2 patient demonstrated an increase in f-VIII levels, also fibrinogen and d-dimer were elevated, while almost all of the antithrombin levels were in the normal range.[1]

Similar study wherein two cases of critically ill COVID-19 patients with HR were diagnosed with raised f-VIII levels and altered aPTT. The condition of these patients enhanced when UFH was replaced with Argatroban. Various alternative anticoagulation regimens have been used in cases of HR, including extreme hemodilution, LMWH (enoxaparin, Dalteparin), danaparoid, ancrod, r-hirudin, abciximab, tirofiban, argatroban and others.Costlier and effective treatment options for HR include administration of antithrombin/fresh frozen plasma which have exhibited remarkable results in patients with HR undergoing cardiopulmonary bypass.[5]

In above mentioned case, due to the easy availability of Dalteparin at our heath care facility, we used that as an alternative to Heparin.The condition of patientimproved spontaneously with a remarkable decrease in the inflammatory markers (IL-6, CRP, d-dimer), which aided our suspicion of HR.

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