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THROMBOSIS IN COVID-19 PATIENTS

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ABSTRACT

COVID-19 has emerged as a global health crisis and it has been very evident from the very beginning that the condition somehow leads to microvascular thrombus formation in the patients, both on arterial and venous level. Thus causing not only multiorgan damage but also cutaneous and pulmonary embolization, strokes, coronary thrombosis etc. which in turn leads to catastrophic outcomes. The mechanisms of these thrombus formation has started becoming evident, with various cascading mechanisms at play, including Virchows traid, immune mediation, cytokine storm, hypoxemia and hypercoagulability etc. Its thus very important to stratify and then target the patients who are at risk of these thrombotic events i.e. elderly, severe COVID-19 disease, comorbidities like less mobility, Diabetes Mellitus, obesity, cancerous patients etc. Stratifying needs to be based on these risk factors as well as D dimer, CT scoring etc. so that they can be given appropriate prophylaxis and treatment if needed.

Patients considered to be at high risk should be placed on high dose heparin therapy as well as studies are being carried out to see if other therapies like antiplatelet drugs, PAI-1 antagonists, tissue plasminogen activators etc. would be of any help.

KEYWORDS: SARS COVID -19; APA antibody antiphospholipid antibody, D-dimer,

Virchows traid; Cytokine storm, PAI-1 Tissue plasminogen activator, ACE receptor .

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نبذة مختصرة:

ظهر مرض كوفيد -19 كأزمة صحية عالمية ، وكان واضحًا جدًا منذ البداية أن الحالة تؤدي بطريقة ما إلى تكوين خثرة الأوعية الدموية الدقيقة لدى المرضى ، على مستوى الشرايين والأوردة. وبالتالي لا يتسبب فقط في تلف العديد من الأعضاء ولكن أيضًا في الانصمام الجلدي والرئوي والسكتات الدماغية والتخثر التاجي وما إلى ذلك مما يؤدي بدوره إلى نتائج كارثية. بدأت آليات تكوين هذه الجلطات في الظهور ، مع وجود آليات متتالية مختلفة في اللعب ، بما في ذلك Virchows traid ، والوساطة المناعية ، وعاصفة السيتوكين ، ونقص الأكسجة في الدم وفرط التخثر وما إلى ذلك ، وبالتالي من المهم جدًا التقسيم الطبقي ثم استهداف المرضى المعرضين لخطر هذه أحداث التخثر ، مثل كبار السن ، ومرض COVID-19 الشديد ، والأمراض المصاحبة مثل قلة الحركة ، وداء السكري ، والسمنة ، والمرضى السرطانيين وما إلى ذلك. العلاج الوقائي المناسب إذا لزم الأمر.
يجب وضع المرضى الذين يعتبرون معرضين لخطر كبير على جرعة عالية من علاج الهيبارين بالإضافة إلى إجراء دراسات لمعرفة ما إذا كانت العلاجات الأخرى مثل الأدوية المضادة للصفيحات ومضادات PAI-1 ومنشطات البلازمينوجين في الأنسجة وما إلى ذلك ستكون مفيدة.

الكلمات المفتاحية: سارس كوفيد -19 ؛ الأجسام المضادة APA الأجسام المضادة للفوسفوليبيد ، D-dimer ، جرثومة عاصفة السيتوكين، منشط البلازمينوجين النسيجي PAI-1 ، مستقبل الإنزيم المحول للأنجيوتنسين.

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INTRODUCTION

Over a year now, humanity has been struggling to get grips with the new SARS COVID-19 virus. It has caused havoc throughout the world. Front liners and students of science are struggling to contain the virus. Medics who usually treat patients with medications only after a whole array of experiments and controlled trials are being forced to give medication and therapies without much knowledge of its effects on the disease process and its effects on the patients and are at the same time learning pros and cons of these new therapies.

COVID on one hand has impacted the widespread social norms of society, economics and on the other hand is creating new challenges each day for its affecties, from the intensive wards to the recovered patients getting new pathological problems, we are all being affected at some level.

DISCUSSION

COVID -19

A mysterious disease originated in China by the end of 2019, this new disease caused by novel coronavirus was named *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2).

On 11 March 2020 WHO declared it as a pandemic. It has spread around the globe with 112.2 million cases till date and we are facing the second wave of the virus presently.

The virus has cause widespread morbidity and mortality, with official mortality figures currently at more than 2.4 million. (WHO COVID-19 data base)

The incubation period for COVID-19 lasts from 2-14 days. Fever, cough, shortness of breath, anosmia, headache, confusion, loss of taste, strokes, chilblains, malaise, sputum production, rhinorrhoea and nasal congestion, as well as gastrointestinal problems are some of the symptoms. In some patient lymphocytopenia and thrombocytopenia are also found and these findings are considered risk factors for developing severe forms of COVID-19. Severe pneumonia, acute respiratory distress syndrome, septic shock and multiorgan failure are main causes of death. (Bleizgys., 2020)

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COVID-19 INFECTING THE CELLS

The coronavirus family have been shown to enter cells through binding to angiotensin-converting enzyme 2 (ACE2) receptors, found mainly on alveolar epithelium and endothelium. Activation of the endothelial cells is thought to be the primary driver for the increasingly recognised complication of thrombosis. (Bleizgys., 2020)

Viral inclusion bodies have been identified in endothelial cells in a variety of organs, from lung to gastro-intestinal tract. (Varga Z, Flammer AJ, Steiger P et al.,2020)

The immune dysregulation characteristic of severe COVID-19 infection may be initiated by 'pyroptosis', a particularly pro-inflammatory form of apoptosis initially described in macrophages (Cookson BT et al.,2001) with rapid viral replication leading to massive release of inflammatory mediators. One of the most consistent findings is that of a raised D-dimer. Although many inflammatory processes can influence D-dimer levels, it almost certainly reflects, to some extent, intra-vascular thrombosis in patients with COVID-19. (Leonard-Lorant et al.,2020) (Cui S et al.,2020)

Although the exact mechanisms of COVID-19 induced thrombosis have not been elucidated, at least some of the well-described mechanisms associated with infection/inflammation are likely to be relevant. (Connors JM et al.,2020)

HYPERCOAGULABILITY IN COVID -19

Hypercoagulability in COVID -19 could be due to several mechanisms:

1. Immune mediated thrombotic mechanisms
2. Complement activation
3. Macrophage activation syndrome
4. Antiphospholipid antibody syndrome
5. Hyperferritinemia
6. Renin angiotensin system
7. Inflammatory mechanism dysfunction
8. Hypoxemia

The profound hypoxaemia that is often observed is a likely driver of vasoconstriction, inflammation and thrombosis. Hypoxaemia will result in activation of hypoxia-inducible factors (HIFs), which in turn will activate cytokines, tissue factor and PAI-1. (Yan SF, Mackman N, Kisiel W et al.,1999) (Gupta N et al.,2020)

Thrombosis has been identified both in acute settings and in weeks following critical illness, suggesting that the pro-thrombotic state could last several weeks or even longer post-hospitalization. (Hanff TC et al.,2020)

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PULMONARY INVOLVEMENT

Pulmonary embolism (PE) and deep vein thrombosis are the most frequently noted thrombotic events in COVID-19, with initial reports noting an incidence of 20% to 30% in critically ill patients. (Hanff TC et al.,2020)

It is highly likely that acute right ventricular dysfunction and cor pulmonale in COVID-19 stem, at least in part, from an abundance of central or segmental pulmonary emboli or a high burden of small vessel pulmonary microthrombi. Prone positioning may help by improving ventilation-perfusion ratio by changing vascular flow distribution in the pulmonary vessels, and not by recruitment as in the case of ARDS. (Sakir Ahmed et al.,2020)

EXTRAPULMONARY AND CARDIAC INVOLVEMENT

Although thrombus has been identified most frequently in the lungs in patients with COVID-19, there is an increasing recognition of extrapulmonary thrombosis that may be a manifestation of de novo thrombus or exacerbation of previous atherosclerotic disease and endothelial dysfunction. (Sakir Ahmed et al.,2020)

Some cardiac involvement in COVID-19 may be related to thrombotic complications. This includes myocardial infarction, in-stent thrombosis, and sudden left ventricular dysfunction, although the incidence of these are unclear and there are a number of non-thrombotic mechanisms that could also underlie cardiac pathophysiology. (Sakir Ahmed et al.,2020)

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) is common in critical illness. Typically, it represents activation of the tissue factor pathway of the coagulation cascade and deposition of platelet-fibrin thrombi in the microvasculature. This eventually leads to the consumption of platelets and procoagulant factors, resulting in an associated bleeding diathesis. (Dhainaut J-F et al.,2005)(Müller MC et al.,2014)

Hypercoagulability in DIC can be exacerbated by features of critical illness itself, including hypoxia, dehydration, and relative immobility. DIC can lead to damage of the microvasculature and subsequent organ dysfunction. While DIC has no specific marker for its diagnosis, it is often characterized by the presence of markedly elevated fibrin degradation products, as is seen in COVID-19. On the other hand, DIC classically has an associated bleeding diathesis that follows from the secondary activation of fibrinolysis, a feature that is not common with other thrombotic microangiopathies (TMA) such as thrombotic thrombocytopenic purpura or catastrophic antiphospholipid antibody syndrome. (Wada H et al.,2004) COVID-19 biomarkers generally suggest idiosyncratic thrombotic pathophysiology that is distinct from DIC, whereas only a small number of laboratory findings in COVID-19 coagulopathy meet DIC criteria.

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MECHANISMS OF THROMBOSIS IN COVID-19

1.VIRCHOWS TRIAD

Comprises of vascular damage, altered blood flow, and hypercoagulability of blood. These factors are active in varying degrees in venous thrombosis. The significance of this triad is that it unifies the inflammatory and the coagulation pathways in the genesis of clotting. (Sakir Ahmed et al.,2020)

The primary function of the endothelium is to maintain the non turbulent blood flow with homeostatic mechanisms to prevent thrombosis and inflammation. (Pober JS et al.,2007)(Teuwen L-A et al.,2020)

The structure of endothelium is different in different tissue as required for specialised function as determined by local need. (Gross PL et al.,2000) The endothelium can undergo considerable proliferative changes as well as plastic changes. (Pearson JD.,2015) Most diseases, including viral infections, affect the vascular endothelium and lead to endothelial dysfunction.

a. Vessel wall abnormalities in COVID-19

The endothelium has a glycocalyx layer and secretes tPA (tissue plasminogen activator) that prevents binding of platelets or initiation of the coagulation cascade.(Pober JS et al.,2007)(Urano T et al.,2012) the SARS outbreak, SARS-CoV virion was detectable in endothelial cells.(Ye J et al.,2007) The ACE2 receptor for SARS-CoV-2 is present in endothelial cells.(Hamming I et al.,2004) Keeping that in mind ,the studies that were done demonstrated SARS-CoV-2 like virion in endothelial cells .(Zhu N et al.,2020)(Varga Z et al.,2020)

The endothelial dysfunction leads to the loss of the fibrinolytic function of these cells, predisposing to thrombus formation. (Suzuki Y et al.,2011) Endothelial disruption leads to massive release on von-Willebrand factor (vWF) from Weibel-Palade bodies that have been reported in COVID-19. (Escher R et al.,2020) All these endothelial factors can initiate thrombosis. The propagation of thrombosis can be aided by the inflammation induced by endothelial dysfunction. Endothelial cells release interleukin-6 (IL-6) in response to the virus invasion that amplifies the host immune response, even to the state of cytokine storm syndrome. (McGonagle D et al.,2020) Though immune complex vasculitis has been postulated as a pathological mechanism for COVID-19, the evidence is limited at present. (Roncati L et al.,2020) Severe COVID-19 leads to a cytokine storm and coagulopathy is a known consequence of acute sepsis. (Semeraro N et al.,2015) This underlying coagulation cascade activation predisposes to sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC).

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b. Abnormal blood flow

Hyperviscosity not only directly predisposes to thrombosis but also induces endothelial injury and dysfunction.(Forconi S et al.,1987) Fibrinogen is a major determinant of blood viscosity, and high levels have been reported in COVID-19.(Bi X et al., 2020)(Han H et al.,2020)(Ranucci M et al.,2020) Fibrinogen-to-albumin ratio (FAR) has been shown to be a predictor of disease progression in multivariate Cox analysis. Another critical area for turbulent blood flow is the microcirculation. The presence of microthrombi and reactionary angiogenesis can lead to impaired microcirculation in COVID-19. (Bray MA et al.,2020)

2. CYTOKINE STORM AND THROMBOSIS

Activation of coagulation and subsequent fibrin deposition is presumably adaptive in the early phase of some other infections, but continued inflammation can quickly lead to a deleterious hyperinflammatory response mediated by cytokine storm and macrophage activation syndrome. Cytokine storm is an auto-amplifying syndrome of proinflammatory cytokine release that is a major contributor to ARDS and multi-organ dysfunction syndrome in several settings, including CAR T-cell therapy and Castleman disease. Macrophage activation syndrome is a related proinflammatory cascade that is associated with a high rate of thrombosis and death in sepsis. (Karakike E et al.,2019) (Crayne CB et al.,2019)

3. COMPLEMENT ACTIVATION

Complement cascade activation may also recruit and activates leukocytes, leading to greatly amplified local release of the proinflammatory cytokines IL-1, IL-6, IL-8, and interferon-γ and subsequent microvascular damage.

Kawasaki-like syndrome reported in children with COVID19 may be due to this immune phenomenon. (Sakir Ahmed et al.,2020)

4. MACROPHAGE ACTIVATION SYNDROME AND HYPERFERRITINEMIA

Macrophage activation syndrome (MAS) may be contributing to aspects of the cytokine storm and hypercoagulable state seen in COVID-19.

As a consequence, there is prolonged interaction between innate and adaptive immune cells that further promotes cytokine storm, hemophagocytosis, and multi-organ dysfunction. Two biomarkers in COVID-19 suggest the potential presence of MAS. The first is elevated IL-6 that is seen in COVID-19 at levels higher than are typical in other viral pneumonias. Second, ferritin elevation is a hallmark sign of MAS, and sustained fever and liver dysfunction are frequently seen in MAS though these are nonspecific. (Sakir Ahmed et al.,2020)

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5. RENIN ANGIOTENSIN SYSTEM OVER ACTIVATION

In comparison to other bacterial and viral pneumonias, inflammation and hypercoagulability in COVID-19 may be uniquely related to its interaction with the renin-angiotensin system (RAS). Infection with SARS-CoV-2 is triggered when the virus binds to angiotensinconverting enzyme 2 (ACE2) similar to what was seen with SARS-CoV. Angiotensin-converting enzyme 2 is a membrane bound protein found in many areas of the body including the lungs, small intestine, heart, brain, adipose tissue, and endothelium. Its distribution is particularly high in the lungs, heart, arteries, and vein. (Walls AC et al.,2020) (Kuhn JH et al.,2020)(Li M-Y et al.,2020)

SARS-CoV-2 exploits ACE2 for cellular entry after using the serine protease TMPRSS2 to prime the viral spike protein. (Hoffmann M et al.,2020) Through this process, it is possible that the pulmonary expression of membrane-bound ACE2 is downregulated. Virus-mediated downregulation of ACE2 would then shift the normal balance towards proinflammatory and prothrombotic effects mediated by Ang II and AT1R. Angiotensin II has several proinflammatory and prothrombotic effects that could be amplified in COVID-19. (Hanff TC et al.,2020)

Increased tissue factor and PAI-1 downstream of Ang II could both lead to a prothrombotic and hypofibrinolytic state. In ARDS, PAI-1 levels are elevated, but the pathophysiologic implication of this has not been firmly established. (Hanff TC et al.,2020)

STRATIFYING HIGH RISK PATIENTS FOR THROMBOSIS IN COVID-19

COVID patients have been presenting with both arterial ie stroke, myocardial infarction and venous thrombosis ie deep vein thrombosis, pulmonary thromboembolism, venous sinus thrombosis.

There is an urgent need to stratifying patients at high risk of thrombosis, these can be divided into:

1. Elderly
2. Comorbidities ie obesity, Diabetes Mellitus, cancerous conditions,immobility, severe COVID -19 disease , pregnancy etc
3. High D-dimer
   An elevated D-dimer at admission (≥1.0 mcg/mL) is associated with an increased mortality with a remarkably high odds ratio of 18.42 (95% CI 2.64-128.55), and D-dimer continues to rise throughout the course of hospitalization in non-surviving patients. This suggests an ongoing coagulopathic state that tracks with disease severity. (Zhou F et al.,2020)
4. Elevations in the prothrombin time (PT) and activated partial thromboplastin time (aPTT) are only modest, and fibrinogen and factor VIII are increased (Cipolloni L et al.,2020) which is more typical of an acute phase response than DIC.

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5. Thrombocytopenia is another feature of COVID-19 that is linearly associated with the risk of death, but the degree of thrombocytopenia observed in late stages of COVID-19 is lower than that which is typically seen in DIC. (Lippi G et al.,2020) (Thiery-Antier N et al.,2016)(Pavoni V et al.,2020)
6. High chest CT (computed tomography) scores
7. High ferritin
8. High PAI-1, IL-6.
9. Nonspecific inflammatory biomarkers are greatly increased in hospitalized COVID-19 patients, including C-reactive protein, erythrocyte sedimentation rate, and ferritin,
10. Procoagulant factors such as von Willebrand factor and Factor VIII. (Cipolloni L et al.,2020) (Fish RJ et al.,2012)
11. Proinflammatory cytokines are increased including tumor necrosis factor alpha (TNF-α) and interleukin (IL)-2R, IL-6, IL-8, and IL-10. Both TNF-α and IL-6, in particular, are elevated to a degree not typically seen in bacterial sepsis or influenza. (Hanff TC et al.,2020)

Which one of these can be used to stratify the at risk group will depend on the availability of the facilities in the particular setting although it prudent to say that D –dimer, ferritin levels, and clotting screen should be atleast sought in all.

MANAGING THROMBOSIS IN SEVERE COVID-19

Considering all of the above mechanisms that lead to thrombosis in the COVID -19 patients and the at risk groups, we can devise a plan to target the thrombosis in these patients on various levels.

These may include:

1.Heparin

2.Tissue plasminogen activator

3.PAI-1 antagonists

4.Antiplatelets

5.RAAS inhibitors

6.Immune therapy

7.Antirheumatic medication

8.Targeting the complement system

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1.Heparin

The initial evidence for mortality benefit with heparin was found in patients with a SIC score ≥ 4 or D-dimer > 6-fold of the upper limit of normal. (Tang N et al.,2020)

Beyond the benefit of anticoagulation, heparin also has antiarrhythmic properties (Menezes-Rodrigues FS et al.,2020) and can even oppose classical RAAS activation. (Ahmed S et al.,2020) The International Society of Thrombosis and Hemostasis (ISTH) have suggested that patients with raised D-dimers (defined as three- to fourfold above the upper range of normal), should be admitted even in the absence of other features because this signifies increased thrombin generation. They have also recommended low-molecular-weight heparin (LMWH) for all admitted patients, including non-critically ill patients. (Thachil J et al.,2020) The problem is that several studies have shown that thrombosis occurs in patients with severe COVID-19 despite LMWH therapy at therapeutic doses. Whether a high dose of heparin is needed in this case is another aspect recent ongoing studies are looking into.

2. Tissue plasminogen activator

Although thrombolysis can be life-saving in myocardial infarction, ischemic stroke, and pulmonary thromboembolism, its usefulness in COVID-19 seems to be still under scrutiny. Small study in COVID-19 patients has been done after tPA infusion, showing oxygen requirements improves, allowing to avoid intubation. (Christie DB et al.,2020) An in silico model has also demonstrated mortality benefit with the use of tPA . There is a proposal to use nebulised tPA for ADRS due to COVID-19. (Sakir Ahmed et al.,2020)

3. PAI-1 antagonists:

These include

1.Angiotensinconverting enzyme inhibitors (ACE-I),

2. Insulin-sensitizing agents (including metformin and thiazolidinediones),

3.Hormone-replacement therapy in women

They can have mild to moderate reduction of PAI-1 levels. There are direct PAI-1 antagonists known, but none has been cleared for human use yet. It may be worthwhile to try APC to maintain the plasminogen pathway in severe COVID-19. (Sakir Ahmed et al.,2020)

4. Antiplatelet drugs

Antiplatelet drugs can potentiate the action of anticoagulation, small studies have been done although still more work needs to be done in this regard to see if this can be used in COVID - 19 patients to any benefit, theoretically the results can seem promising but further studies are awaited. (Sakir Ahmed et al.,2020)

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5. RAAS inhibitors

There is controversy regarding the use of ACE1- inhibitors (ACE-I) and angiotensin II-receptor blockers (ARBs) in patients with COVID-19 since both are known to increase ACE2 level that is the receptor for SARS-CoV-2. However, since the primary pathology is due to the loss of ACE2, it stands to reason that ACE-I and ARBs can be helpful. (Vaduganathan M et al.,2020)

Both losartan and Ramipril have synergistic antiplatelet action when given with dual antiplatelet drugs given postmyocardial infarction. Thus, ACE-I/ARBs can potentiate other antithrombotic therapies in COVID-19. (Marinšek M et al.,2016) (Sakir Ahmed et al.,2020)

6. Targeting complement:

Eculizumab can be successfully used in COVID-19. (Sakir Ahmed et al.,2020) Some small studies have been done and others are ongoing to see if this can be used for the COVID-19 patient.

7. Immune therapy:

While interventions such as intravenous immunoglobulin 9 (IVIg) therapy may save lives of patients with Kawasaki like syndrome, its use may also increase thrombosis risk. This risk may be due to increased blood viscosity or due to factor (F) XI in substantial quantities in the IVIg products. (Sakir Ahmed et al.,2020)

8.Antirheumatic drugs:

The use of various disease-modifying antirheumatic drugs (DMARDs) has been suggested for COVID-19 . There is controversy about the utility of hydroxychloroquine (HCQ) in COVID-19. The prolonged use of HCQ in systemic lupus erythematosus and rheumatoid arthritis proved effective for reducing cardiovascular risk. HCQ has been shown to reduce levels of tissue factor and related thrombotic pathways in antiphospholipid syndrome. (Sakir Ahmed et al.,2020)

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CONCLUSIONS

1. A high index of clinical suspicion for thrombotic phenomenon and their sequela is warranted for prompt diagnosis. Clinical signs and symptoms of thrombosis. such as cutaneous manifestations like “COVID toe” (Seirafianpour F et al.,2020) overt line thrombosis, arterial or venous clots, unexplained increase in oxygen requirement, or organ dysfunction should raise suspicion and prompt further investigation and/or discussion about therapeutic intervention. (Klok FA et al.,2020)
2. Its important to routinely monitor platelet count, PT/aPTT, d-dimer, and fibrinogen to assist in anticipating and managing thrombotic complications. It has been reported that d-dimer levels cutoff of 1.5 μg/mL for predicting venous thromboembolic events has a sensitivity and specificity rate of 85% and 88.5% respectively and a negative predictive value of 94.7%. (Samhati Monda et al.,2020) Nonetheless, decisions for initiation of therapeutic anticoagulation should not be based solely on arbitrary d-dimer levels.
3. Use of viscoelastrometric tests such as Rotational thromboelastometry (ROTEM) could also be used as an important monitoring tool. Short clot formation time (CFT) on INTEM (type of ROTEM to detect Intrinsic pathway abnormality) and EXTEM (type of ROTEM to detect Extrinsic pathway abnormality) and increased maximum clot firmness (MCF) on INTEM, EXTEM, FIBTEM (type of ROTEM to detect fibrinogen. (Klok FA et al.,2020)
4. In asymptomatic and mildly symptomatic patients who do not require hospital admission, ambulation should continue to be the mainstay of thromboprophylaxis. It is advisable to institute, at minimum, prophylactic anticoagulation in admitted patients without clinical contraindications. (Bikdeli B et al.,2020)
5. Unfractionated heparin and low molecular weight heparin (LMWH) have been successfully used in patients both prophylactically and therapeutically. Higher doses should be considered for those with higher risk patients (eg, obese, active malignancy, prolonged immobility or recent surgery). (Klok FA et al.,2020)
6. Active surveillance for thrombosis should continue even after initiation of therapeutic anticoagulation as clot progression has been demonstrated in patients with therapeutic levels of anticoagulation. Patients with COVID-19 who experience a major thromboembolic event such as PE without any additional risk factors should be considered to have had a “provoked thromboembolic event” and may need 3-6 months of anticoagulation. (Streiff MB et al.,2016) Minor episodes of DVTs should continue anticoagulation therapy for 2-6 weeks post hospital discharge . The optimal duration of anticoagulation for those with risk factors, either new or pre-existing risk factors (eg atrial fibrillation) may need to be modified according to established guidelines.

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7. Long term follow up data on thrombotic risk post hospital discharge however remains unclear at this point. Antiviral therapies, which may be utilized in certain COVID-19 patients, are potent enzymes inhibitors and can slow down metabolism and prolong duration of action of many medications including direct oral anticoagulants so caution should be exercised regarding their concomitant dosing. (Samhati Mondal et al.,2020)
8. Prophylactic anticoagulation should be considered in patients presenting with elevated d-dimer levels but with no suspicion or evidence of thrombosis. Decisions on discharge therapy should be based on hospital protocols, patient specific factors, and multidisciplinary discussions regarding the risk benefit profile of chosen strategies. (Klok FA et al.,2020)
9. Oral anticoagulants, including warfarin, the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and betrixaban, should not be considered for the treatment of thrombosis in COVID-19 patients, because of possible interactions with antiviral therapeutics. (Bikdeli B et al.,2020)
   It must be noted that a high incidence of VTE has been noted even on patients on either prophylactic and therapeutic anticoagulation, which makes routine surveillance extremely important. (Sakir Ahmed et al.,2020)

RECOMMENDATIONS

Although lot of research has been done to know the association between the thrombosis and COVID-19 , we still have a long way to go before we can get the the bottom of the accurate mechanisms .Its thus recommended that in the meantime as per lots of studies done, we should be identifying the high risk patients in the cohort of COVID-19 and these high risk patients should be provided with proper thromboprophylaxis .

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