Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Argatroban for the Management of Heparin induced thrombocytopenia in COVID-19 Cases

Sir, — We congratulate A Chandra *et al* for their case report on Thrombocytopenia in COVID-19. The situation of thrombocytopenia in COVID-19, poses a great diagnostic and therapeutic challenge in addition to it being a predictor of bad prognosis. Mild thrombocytopenia is common, but if there is severe thrombocytopenia while on heparin, one has to consider Heparin Induced Thrombocytopenia (HIT). As the patient showed sign of acute kidney injury Low Molecular Weight Heparin (LMWH) had been switched to Unfractionated Heparin (UFH). Heparin induced thrombocytopenia is more likely with UFH than with LMWH. As per Patell *et al* the prevalence of HIT antibodies is higher than in other situations[1].

Both the factors, COVID-19 infection and HIT, are prothrombotic state. It is a real dilemma how to manage venous thromboembolism in presence of thrombocytopenia. As per few case reports and literature, direct thrombin inhibitors may be considered for anticoagulation. The anticoagulants in this category are fondaparinux, argatroban, danaparoid and bivalirudin. Ogawa et al and Lingameneni et al had successfully managed a case each with argatroban[2,3]. Argatroban has a short half life of 24 minutes and require parenteral infusion at a rate of 1-2mcg/kg/minute. It requires monitoring to keep a target aPTT of 1.5 to 3 times the initial value. One has to consider the risk of bleeding as Patell et al found that 3 of their patients had developed major bleeding. If there is a risk of bleeding it may be initiated at a much lower dose, especially if the patient has liver dysfunction.

References

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A Comparative Study of the biochemical components of Human Umbilical Cord Blood and Adult Peripheral Blood

Sir, — Human umbilical cord blood is a massive and potential resource useful in combating many chronic diseases like anemia, leprosy, tuberculosis etc. Cord blood, being fetal in nature, is predominantly rich with hematopoietic stem cells, enriched with cytokines, growth factors and progenitor cells that can have a profound effect against chronic diseases, genetic disorders and many more. This study aimed to determine whether there was any difference between the biochemical components of Human umbilical cord blood & adult peripheral blood. 5 test samples are taken from both the Human umbilical cord blood and the adult peripheral blood and first undergo microscopic examination through a blood smear test to determine the size, shape and different types of blood cells. Secondly, hematological examination such as CBC, ie, Complete blood count, haematocrit value. Thirdly, serum metabolites value (like glucose, albumins, bile acids, bilirubin, cholesterol etc) Also, cytokine studies such as IL-6 (Interleukin- 6) determine whether it acts as a pro-inflammatory or anti-inflammatory cytokine. This study should be conducted in every institute for the betterment of Human race. It is a futuristic medicine approach through which we can achieve some of the greatest things of all time. This modern medicine study shows you what we can use from the garbage material to turn it into gold.

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Colchicine In COVID-19

Sir, — As wave after wave of the COVID-19 pandemic catches us off guard, more than ever is the need for a medicine that can rapidly, effectively, and decisively, changes the course and turn the tide of this devastating disease. The authors, hereby, wish to discuss the role of Colchicine for COVID-19 disease.

Colchicine is an alkaloid derived from the bulb-like roots of plant *Colchicum autumnale,* also known as *Autumn crocus*. Traditionally, it has been specifically used for suppressing gouty inflammation, for which it has been credited to be the fastest drug to control an acute attack[1]. Dose is 0.5mg 1-3 hourly, with a total of 4 doses in a day; maximum 6 mg in a course spread over 3-4 days may be given[1]. The response is dramatic, and may even be considered diagnostic. It is also used in Familial Mediterranean fever, Behcet's disease, pericarditis and atrial fibrillation[2].

Colchicine suppresses the inflammatory response by[1,3] : (a) preventing granulocyte migration to the site of inflammation, (b) inhibiting the release of glycoproteins, which is responsible for aggravating inflammation by forming lactic acid and releasing lysosomal enzymes,

(c) binding to intracellular protein 'tubulin', and causing depolymerization and disappearance of microtubules in granulocytes, causing metaphase arrest. As a result of this, migration of granulocytes into the area of inflammation is not only distorted but prevented, thereby interrupting the vicious cycle. Colchicine treated neutrophils develop a "*drunken walk*". Colchicine has the distinctive feature of accumulating in inflammatory cells at the site of inflammation, and reaching a higher concentration than plasma levels, with a markedly longduration of action[4]. It is rapidly absorbed orally, undergoes enterohepatic circulation and ultimately is disposed in urine and feces over many days[1,3]. Concurrent use of inhibitors of CYP3A4 and P-glycoprotein such as erythromycin, tetracycline, grape fruit juice, lopinavir and ritonavir, ketoconazole, diltiazem, verapamil, cimetidine, amiodarone, tamoxifen, quinidine, tacrolimus and cyclosporine can cause colchicine toxicity[2].

Colchicine has a narrow therapeutic index and toxicity is dose related. Nausea, vomiting, diarrhea and abdominal cramps (neurogenic stimulation of gut motility) occur as dose limiting adverse effects. Accumulation of the drug in intestine and inhibition of mitosis in its rapid turnover mucosa is responsible for the toxicity. In overdose, colchicine produces bloody diarrhea, throat pain, kidney damage, CNS depression; death is due to muscular paralysis and respiratory failure[1,3].

For COVID-19 disease, currently, oxygen, steroids and low molecular weight heparin have been the most used drugs, at a time when we still search for an anti-viral that can actually make a difference. With the experience of more than one year, it has been seen that the best time to start a steroid is the onset of inflammatory phase when hypoxemia starts setting in, with or without breathlessness. But like all medicines, steroids too have their limitation in terms of wide array of side effects that they cause. Their effect is non-specific and covers all components and stages of inflammation[1].

Ten colchicine clinical trials are currently in various stages of progress for the treatment of SARS-CoV-2 treatment and are listed on clinicaltrials.gov[4]. They differ in the timing of initiation as well as the dosing of colchicine. Some studies begin treatment in the outpatient setting and others in early inpatient setting. Dose varies from 0.5mg twice daily for three days followed by 0.5 mg for next 27 days to others like 0.5 mg or 0.6mg twice daily for 14 days or until discharge. Colchicine is cost effective and can prove to be a game changer when given during the early pulmonary phase of COVID-19, coinciding with the rise of inflammatory markers like CRP (C-reactive protein) and worsening of radiological severity. One suchrandomized controlled trial conducted in 2020 in adults with moderate or severe forms of COVID-19, with a total of 72 patients (including placebo group), showed improvement in terms of need for oxygen and length of hospitalization[5]. Researchers used the dose of 0.5 mg thrice daily for 5 days, then 0.5mg twice daily for next 5 days; if body weight was more than or equal to 80 kg then first dose was 1 mg. Dose was reduced in chronic kidney disease. Majority of adverse events were mild. While new or worsened diarrhea was more frequent in intervention group (17% *versus* 6%), none of the patients suffered dehydration, and the diarrhea was controlled with prescription of an anti- secretory drug (ex. racecadotril).

It is hereby proposed that colchicine may be considered in moderate COVID disease as the first anti-inflammatory agent, to which steroid may be added later as hypoxemia worsens. It may be given in both outpatient and inpatient setting, especially in high risk individuals by informed clinicians.

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