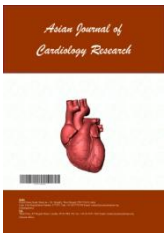

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A Hypothetical Intervention to Prevent Acute Myocardial Injury among Patients with Ischemic Heart Disease and SARS-CoV-2 Infection

Kolitha H. Sellahewa[1,2*], Dhilmi Suriyarachchi[3] and Tharindu Ruwanpathiranage[4]

[1]General Sir John Kotelawala Defence University, Rathmalana, Sri Lanka.
[2]Department of Internal Medicine, Neville Fernando Teaching Hospital, Millenium Drive, Malabe, Sri Lanka.
[3]District General Hospital Polonnaruwa, Sri Lanka.
[4]National Hospital, Colombo, Sri Lanka.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Acute myocardial injury in SARS-CoV-2 infection results from myocarditis and coronary thrombosis initiated by destabilisation of existing and newly generated plaques. Appropriately timed dual antiplatelet therapy with statins early in the disease course is a hypothesised preventive management pathway.

Keywords: Acute myocardial injury; dual antiplatelet and statin therapy in SARS-CoV-2 infection.

**Corresponding author: Email: kolithah@gmail.com;*

1. INTRODUCTION

More than 3 million deaths have now been reported worldwide due to the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic [1]. Increased cardiovascular morbidity and mortality are well recognized with respiratory viral infections such as seasonal influenza and outbreaks of SARS and MERS, with up to a 6-fold increased risk of acute myocardial infarction [2,3,4]. Cardiac involvement has been identified as a consequence of the SARS-CoV-2 pandemic from its very beginning [5].

Worldwide, increased prevalence of cardiovascular disease and coronary artery disease has been reported in COVID-19 patients, with studies in China reporting prevalence rates of myocardial infarction between 4.2% to 25%, and higher rates in those admitted to ICUs [6,7]. In addition, patients with previous cardiovascular comorbidities have shown to develop severe disease, and deaths are higher among such COVID-19 patients [5,7]. During outbreaks an increased incidence of out of hospital cardiac deaths and late presentation myocardial events are observed with worse outcomes [8].

In Sri Lanka, among confirmed COVID-19 deaths with comorbidities, 21.3% of deaths are from ischaemic heart disease (IHD) and 14% are in the 30-60year age category [9].

Overall, both worldwide and local data show a substantial increase in morbidity and mortality among patients with IHD and SARS-CoV-2 infection. Hence, a judicious strategy in managing patients with background IHD is essential. We have conceptualised a preventive strategy as guidelines WHO [10] & National guidelines - Ministry of Health Sri Lanka [11] have not addressed specific management pathways to prevent mortality and morbidity in patients with IHD having SARS-CoV-2 infection.

2. PATHOGENESIS

Infection with the novel coronavirus has a distinctive clinical course comprising viremic and immunological phases. Clinical manifestations of invasion of host cells and viral replication early in the disease course are fever, cough myalgia, lassitude, throat irritation, anosmia and ageusia. This phase lasts about 7 days [12]. The advent of a protective immune response is associated in most patients with defervescence and resolution. However, in some patients a cytokine storm resulting from an exalted immune response is a severe disease, manifesting primarily with respiratory distress [13].

Acute myocardial injury (AMI) may occur in both viremic and immunological phases of the disease. SARS-CoV-2 virus though primarily affecting the respiratory system may cause multi-organ dysfunction as a consequence of systemic viral dissemination and direct tissue injury. Myocardial injury during the viremic phase manifesting as myocarditis is well recognized [14,15]. Sheer forces generated by coronary vasoconstriction during viremia are known to cause endothelial damage and adhesion of platelets to the altered vascular endothelium which may initiate platelet aggregation and eventual generation of platelet fibrin thrombi [16].

Inflammatory mediators cause rapid onset of new plaques and destabilization of pre-existing coronary arterial plaques which predispose to thrombus formation. Release of thrombotic inflammatory mediators facilitates the propagation of these thrombi and cause acute ischaemic coronary events [17]. Hence, myocardial injury by two independent mechanisms is a distinct possibility during the viremic phase of the disease.

Compounding the problem is the propensity for further myocardial injury during the immunological phase. Dysregulated immune response results in a cytokine storm and an overwhelmed inflammatory response that aggravates the tendency for coronary thrombosis and ischaemic myocardial injury [17,18,19]

In COVID-19 patients, acute cardiac events may occur early in the viremic phase as well as late in the immunological phase of the disease course owing to the complex interplay of different pathophysiological mechanisms. Two essential mechanisms of AMI are implicated. One is direct injury by viral myocardial invasion, and the other by myocardial hypoxia. Myocardial hypoxia results from coronary vasoconstriction, thrombotic occlusion and arterial hypoxemia from associated covid pneumonia, which is invariable in the setting of a dysregulated immune response. The resulting tachycardia, apart from compromising coronary filling, increases the oxygen demand and aggravates myocardial hypoxia.

Recognition of these fundamental pathogenic mechanisms of AMI in COVID-19 is of crucial

importance in the prevention of adverse and sometimes fatal outcomes by timely, appropriate, specific interventions.

3. HYPOTHESIS

It is our hypothesis that critically timed and judiciously selected interventions with antiviral, antiplatelet, antithrombotic, anti-inflammatory drugs as well as statins, beta blockers and nitrates would prevent AMI and enhance favourable outcomes in COVID-19 patients with associated IHD.

4. REVIEW OF PUBLISHED DATA

The management of COVID-19 is grounded on interventions designed to act at different stages in SARS-CoV-2 infection. Recognition of thromboembolism and its related complications in SARS-CoV-2 has made anti-thrombotic drugs essential in the management of both mild and severe pneumonia [10]. The early use of enoxaparin as initial therapy has shown decreased mortality among patients hospitalized with COVID-19 [20]. However, there is no substantial evidence to justify the use of prophylactic anti-thrombotics in asymptomatic patients and patients with mild symptoms.

Aspirin, well known for its antiplatelet properties has shown potential to be used as a useful therapeutic intervention in COVID-19, as meta-analysis shows a reduction in risk of a fatal course of COVID-19 with the use of aspirin [21]. Retrospective analysis shows a significant decrease in mortality in patients who were on aspirin prior to the diagnosis of COVID-19 [22]. The use of aspirin along with clopidogrel and other antiplatelet drugs was explored in a case control study that observed their superior effects in improving oxygenation and other parameters [23].

Patients already on statin therapy have been allowed to continue their medication during the course of illness. Retrospective studies show a 50% reduction in the risk to develop severe COVID-19 where statins had been used 30 days prior to admission [24]. Reduced mortality has been shown in a meta-analysis of thirteen studies in which in-hospital COVID-19 patients used statins [25]. And recent studies have reaffirmed the beneficial effects of statins in reducing in-patient mortality [26]. Furthermore, statin related liver injury has been shown to be uncommon [27].

5. MANAGEMENT STRATEGY

Clear understanding of the disease course, pathogenesis of cardiac injury and the phases of the disease are central for rational interventions. Hence, a prerequisite for better case management is the day of illness at the time of presentation. This should be determined as accurately as possible by inquiring for the day on which the symptoms first started. Some of the common symptoms early in the disease are; fever, cough, myalgia, lassitude, anosmia, aguesia and throat irritation. That should be regarded as day 1 and subsequent clinical events correlated appropriately to this timeline. Breathlessness at rest or slight exertion, tachypnoea and arterial hypoxaemia are late features. Interventions must precede the occurrence of these clinical features to ensure a favourable outcome.

6. VIREMIC PHASE

Attempts must be made to reduce the viral load by early antiviral treatment of proven benefit. However, antivirals such as ivermectin and remdesivir have not shown substantial evidence for benefit and the current recommendation does not favour their use [28]. Hydroxychloroquine is best avoided owing to the risk of QT prolongation and its possible consequences on patients with IHD [29].

The generation of new plaques and rupture of existing plaques may take place during this phase. Aggressive interventions directed towards plaque stabilization and inhibition of platelet function should dominate the treatment early in the disease course. High dose statins and dual antiplatelet therapy started early is likely to effectively attenuate the tendency for thrombosis and myocardial injury from ischemia. Aspirin is a good choice. In addition to its antiplatelet effects, its early use gives the added benefit of its antiviral and anti-inflammatory properties [20]. Aspirin should be the first choice of the antiplatelet medication unless there is a contraindication for its use such as allergy, risk of bleeding or co-infection with dengue. Aspirin should be combined with another antiplatelet agent with a different mode of action to minimise the chance of platelet fibrin thrombi formation in the setting of altered vascular endothelium and its propensity for platelet mediated thrombogenesis. Aspirin by irreversible acetylation of Ser 530 of COX-1 inhibits platelet generation of thromboxane A2. P2Y12 inhibitors

(ticagrelor, clopidogrel,pasugrel,and ticlopidine) on the other hand prevent activation of glycoprotein IIb/IIIa receptor complex and thereby attenuate the risk of thrombus formation by inhibiting platelet aggregation. Dipyridamole though not commonly used for dual antiplatelet therapy in IHD, is the choice to be combined with aspirin in COVID-19 patients as it has also been shown to directly suppress SARS-CoV-2 based on in silico docking and in vitro cell culture studies [30].

High dose statin should be used early in the disease primarily to stabilize the newly generated plaques in COVID-19 and pre-existing plaques that tend to rupture during infection.

Recognition of plaque rupture and platelet activation as the initiators of the clotting cascade provide compelling reasons for early aggressive intervention with dual antiplatelet and high dose statin therapy. Such an intervention will not only prevent coronary thrombosis but will also serve to attenuate the tendency for pulmonary arterial occlusion by in-situ thrombogenesis and the resulting arterial hypoxemia from V/Q mismatch [31,32]

Patients with chronic IHD are usually on a combination of antiplatelet drugs, beta blockers, angiotensin converting enzyme inhibitors and statins for secondary prophylaxis against myocardial infarction. However despite guideline advocacy some patients may not be taking these drugs owing to poor follow-up, failure to recognise the need for compliance when symptom free after recovering from an acute coronary event as well as economic constraints. The described interventions become increasingly important for such patients in the event they contract COVID-19 owing to the increased propensity to develop myocardial injury in such a setting. Our emphasis is on the need to restart early, dual antiplatelet therapy and statins in the event of a patient with chronic IDH, and not on these prophylactic medications develops COVID-19.

7. IMMUNOLOGICAL PHASE

Dual antiplatelet therapy and statins started in the viremic phase should be continued. The recognised anti-inflammatory and immunomodulatory features of statins are added benefits for continuation. The hyperactive inflammatory response could be mitigated at inception before progression to cytokine storm by rational application of the pleiotropic properties of statins [33,34,35].

Additional protection against thrombosis should be achieved with enoxaparin as the tendency for thrombosis is enhanced during this phase of the disease from release of thrombogenic inflammatory mediators.

Combating the cytokine storm must dominate the interventions at this stage. Immunosuppression with steroids such as dexamethasone or equivalent doses of methyl prednisolone, hydrocortisone or prednisolone are all of proven benefit [36]. Dexamethasone may be harmful in AMI, but in patients with both COVID-19 and IHD its capability in attenuating the cytokine storm at its inception and conceived prevention of progression to severe COVID pneumonia and hypoxia may be more beneficial. It is a critical decision the attending physician should take in providing individualised care in complex clinical situations with acute life-threatening comorbidities by balancing benefit against harm.

Recent randomised trials show survival benefits in the use of Janus kinase inhibitor barcitinib or the interleukin-6 pathway inhibitor tocilizumab in hospitalized adults with severe COVID-19 [27].

Liberal use of beta blockers (unless contraindicated) and nitrates are recommended during all stages of the disease. Tachycardia in COVID-19 patients can aggravate coronary ischaemia. Beta blockade also provides haemodynamic benefit by moderating the dynamic left ventricular outflow tract obstruction in patients developing apical myocardial injury and attended hypokinesia relative to the outflow tract. Selection of patients for this indication should be based on a correlation of electrocardiographic changes of myocardial infarction with the deduced territory of infarction, as access for echocardiography to detect accurately dyskinetic segments of myocardium is not readily available for COVID-19 patients.

Even in the absence of ischaemic chest pain nitrates will be useful add on therapy for its coronary vasodilator properties to minimise the adverse consequences of coronary vasoconstriction recognised in COVID-19.

. SUMMARISED GUIDANCE ON MANAGEMENT

➢ ***Presentation before 7 days of illness – Viremic phase***

1. Continue the underlying medication in the same doses if the patient is already receiving anyone or more of the following drugs:
    a. Beta blockers
    b. Calcium channel blockers
    c. Nitrates
    d. Any other drugs for IHD

2. Add on therapy(if not already taking these drugs for chronic IHD)
    a. Atorvastatin 40 mg stat and 40mg daily irrespective of lipid status. This therapy is mandatory and should be prescribed for all patients with coronary artery disease irrespective of their clinical status or ECG findings, unless there is a contraindication for its use.
    b. Aspirin 75 mg daily - Do NOT use if there is allergy to aspirin
    c. Dipyridamole 100mg TDS (ticagrelor or clopidogrel are options based on physician preference. Dipyridamole is suggested because of recognized direct suppression of SARS-CoV-2 apart for antiplatelet effect)

3. Admit the patient to HDU to facilitate dedicated closer monitoring among other COVID-19 patients without pre-existing IHD
    a. Vigilance and monitor to detect complications
    b. Ensure adequate hydration

➢ ***Presentation after 7 days – Immunological phase***

1. Check bio markers of inflammation
    a. CRP
    b. LDH
    c. FBC - N/L ratio
    d. Serum ferritin
    e. Troponin
2. Check peripheral SpO2 with pulse oximeter

Suggestive of an exalted immune response with inflammation and incipient cytokine storm

Initiate an aggressive pharmacologic interventional pathway to attenuate SARS-CoV-2 mediated pathogenic mechanisms implicated in myocardial and other vital organ hypoxia

- Dual antiplatelet therapy
    - Aspirin + Ticagrelor(or Clopidogrel)
- Anticoagulation
    - Enoxaparin prophylactic dose adjusted to estimated glomerular filtration rate
- Plaque stabilization
    - Atorvastatin
- Anti-inflammatory immunosuppressive agents(Do NOT use NSAIDs)
    - Dexamethasone

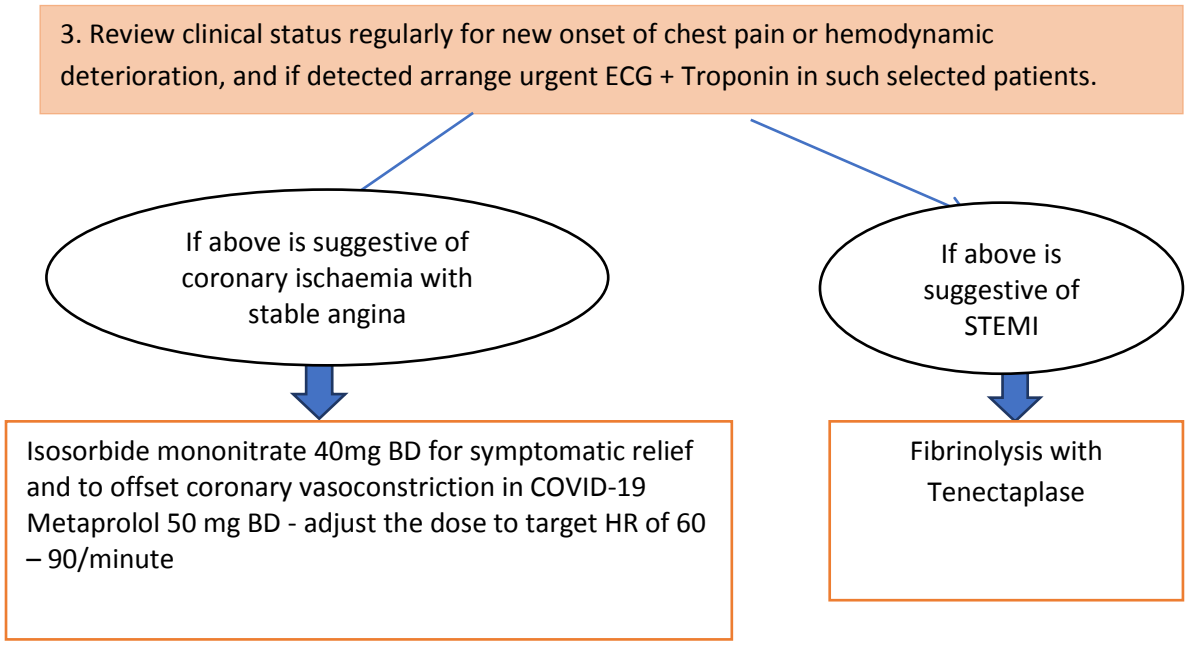

Fig. 1. Immune response with inflammation and incipient cytokine storm

9. CONCLUSION

The high mortality among patients with IHD contracting COVID-19 is well recognised. Clear guidance on managing these patients to prevent deaths is not available. The pathogenesis of the disease is now well known and published. Published data has addressed distinct mechanisms of AMI in SARS-CoV-2 infected patients. This evidence provided the basis for a proposed preventive strategy based on a correlation of disease pathogenesis and mechanisms of AMI with known pharmacological therapies conventionally used in managing IHD, including acute coronary events.

Interventions are essentially evidence based treatments. Emphasis is on the early use of dual antiplatelet therapy and statins with a view to stabilise existing and newly generated plaques and the inhibition of platelet adhesion and aggregation that initiates the clotting cascade. Such an aggressive approach targeting multiple sites of action in thrombus generation is likely to prevent the generation of thrombi, not only in the coronary arteries but also in the pulmonary vasculature and other vital organs.

Interventions are augmented down the time line of the disease course as appropriate; with steroids, enoxaparin, tocilizumab etc. as per accepted protocols on management of COVID-19 patients with moderate and severe disease based on the extent of respiratory distress and SpO2. But we believe that the early use of antiplatelet drugs and statins could prevent in-situ thrombus formation in pulmonary arteries and impact a favourable shift in the V/Q mismatch responsible for arterial hypoxia.

We have developed an algorithm to be applied on an individualised basis to guide patient care with the primary objective of preventing AMI. We recommend clinicians to use this algorithm proactively in individualizing care by the judicious application of known therapeutics rationally, to offset identified pathogenic pathways of AMI. We believe that these interventions at the inception of inflammation early in the disease course, before the advent of a cytokine storm, could have the greatest beneficial impact in reducing mortality by preventing cardiac as well as other vital organ dysfunction.

Our hypothesis should be tested by well-designed carefully controlled case studies. However its application on an individualised basis should not be precluded awaiting the completion of case studies as there is a void of clearly identified pathways of care to prevent AMI specifically in COVID-19 patients with IHD.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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