Iloprost: a potential treatment for COVID-19 related vasculopathy

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Word count: 730

Supplementary Table: 1

Supplementary Figures: 2

References: 10

Coronavirus disease 2019 (COVID-19) is presenting an unparalleled challenge for clinicians. In critical cases, the combination of severe inflammation, systemic coagulopathy, and acute respiratory failure results in a multisystem illness with high morbidity and mortality. The coagulopathy associated with COVID-19 has been associated with high rates of pulmonary embolism, myocardial infarction, ischemic stroke, digital ischemia, and renal failure, despite prophylactic anticoagulation.[1,2] The hypercoagulable state associated with SARS-CoV-2 is thought to be the result of endothelial cell dysfunction secondary to endotheliitis.[3] Endotheliitis causes vasoconstriction, altered barrier permeability, and a pro-coagulant state. Here, we explore the potential of iloprost as a therapy to mitigate the pathological effects of COVID-19, describing three patients who benefited from its use. Its potential ability to reduce endothelial dysfunction and systemic inflammation could make iloprost a key player in managing COVID-19 vasculopathy.

Iloprost is a prostacyclin receptor agonist that promotes vasodilation of circulatory beds with minimal impact on haemodynamic parameters. It is licensed for the treatment of pulmonary arterial hypertension, and widely used for the management of peripheral vascular disease and digital vasculopathy, including digital ulcers and critical digital ischemia in systemic sclerosis.[4,5] Iloprost is anti-thrombotic, anti-inflammatory, and anti-fibrotic, exerting these effects via inhibition of platelet activation and suppression of IL-6 and TNF-alpha production.[6,7] Autopsy studies have shown that endotheliitis and microvascular thrombi in pulmonary capillaries are part of the disease pathogenesis in COVID-19.[8] By restoring healthy endothelial function, iloprost may minimise the lung damage and thrombotic complications seen in COVID-19. It is increasingly recognized that peripheral vascular insufficiency occurs in some cases, leading to acrocyanosis and chilblains.[8] Systemic iloprost, given as a low-dose continuous infusion, is often used in patients with autoimmune peripheral vasculopathy.[5,9] Given its efficacy and its favourable safety and tolerability profile,

it is an attractive candidate for use in COVID-19. Based on this rationale, we added iloprost to standard treatment in three patients with COVID-19.

Three patients were admitted to hospital with severe COVID-19 disease, defined as acute onset of bilateral lung infiltrates, and hypoxemia requiring >40% FiO_2 to maintain saturations above 94%. All had positive RT-PCR nasopharyngeal swabs for SARS-CoV-2. Two patients presented with clinical evidence of digital ischaemia and the third developed changes during hospital admission. The patients were all male, had a median age of 46 years (range 46-62), and all suffered from morbid obesity. Full demographic and clinical characteristics are shown in the Supplementary Table. All three patients were commenced on supportive treatment with oxygen via a Venturi mask and fluids, prophylactic anticoagulation, and intravenous co-amoxiclav. Two also received oral clarithromycin. The mean SOFA score was 6 (range 5-7), and the mean initial pre-iloprost PaO_2/FiO_2 ratio was 154·6 (range 152-158). The decision to start a five-day intravenous infusion of iloprost was based on an expert clinical diagnosis of digital ischemia by the treating consultant and a persistent oxygen requirement that likely reflected systemic microvasculopathy.

After a continuous five-day infusion of 0·5 micrograms/kg/min, we noted a sustained clinical improvement in the digital ischemia, as well as in cardiovascular and respiratory parameters. In all patients, decreasing oxygen requirements, increasing PaO_2/FiO_2 ratios, and normalisation of heart rate were seen up to 48h after the cessation of the iloprost infusion (Supplementary Figure 1). None of the patients required mechanical ventilation during their hospital admission and all tolerated the iloprost infusion well with no bleeding complications or serious adverse events to warrant cessation. One patient experienced diarrhoea during the infusion that terminated upon iloprost withdrawal. Notably, upon cessation of iloprost on day five, a mild rebound tachycardia and transient worsening of symptoms was observed, but this

resolved before discharge in all patients. One patient's hospital course was complicated by pulmonary embolus which required a longer stay but remained stable and was discharged on rivaroxaban.

This case series illustrates that iloprost may be a useful adjunctive therapy for COVID-19 vasculopathy, improving digital ischemia as well as cardiorespiratory parameters. Inhaled iloprost has been shown to improve ventilation parameters through its vasodilatory effects, thereby improving gas exchange.[10] Furthermore, systemically infused iloprost might also improve ventilation/perfusion matching in the lung, leading to the effects observed in our patients. Although larger controlled studies are needed to confirm our observations and despite the limitations inherent to small case series, based on the pharmacological effects of iloprost in analogous pathological states and its favourable safety profile, we suggest that iloprost may be a useful adjunctive treatment in COVID-19.

Contributors

CJM: concept, data collection, analysis, figures, revisions, and writing
AJX: data collection, analysis, figures, revisions, and writing
AA, SH: data collection, analysis, writing
CD, RS: concept, supervision and writing

All authors approved the final draft.

As corresponding author, I confirm that I had full access to the data in the study and had final responsibility for the decision to submit for publication.

All patients included in this study provided written and verbal informed consent for publication of the paper and the supplementary materials

Declaration of interests

We declare no competing interests.

Funding sources

None declared.

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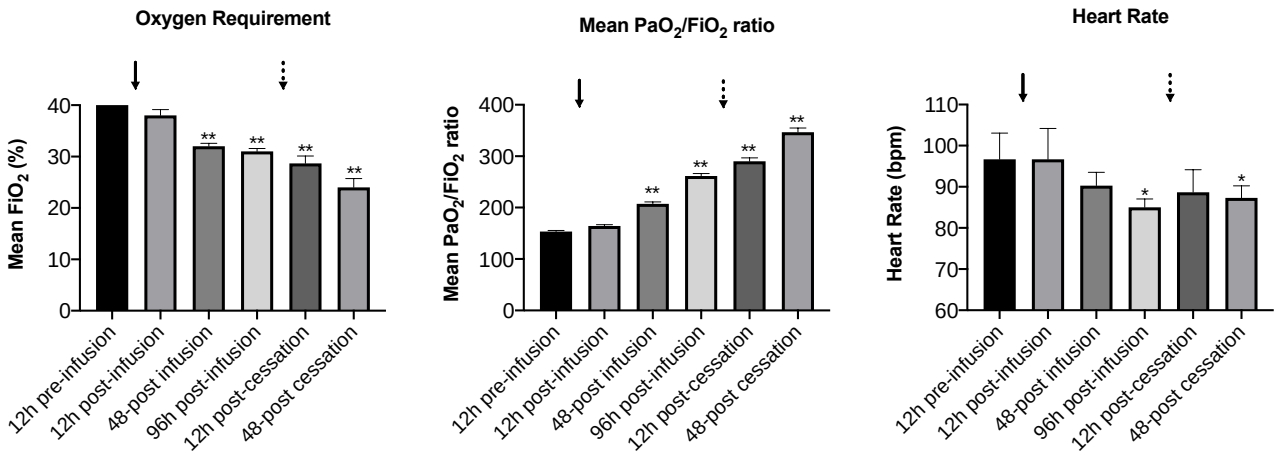
Supplementary Appendix

Supplement to: Moezinia CJ, *et al.* Iloprost: a potential treatment for COVID-19 related vasculopathy.

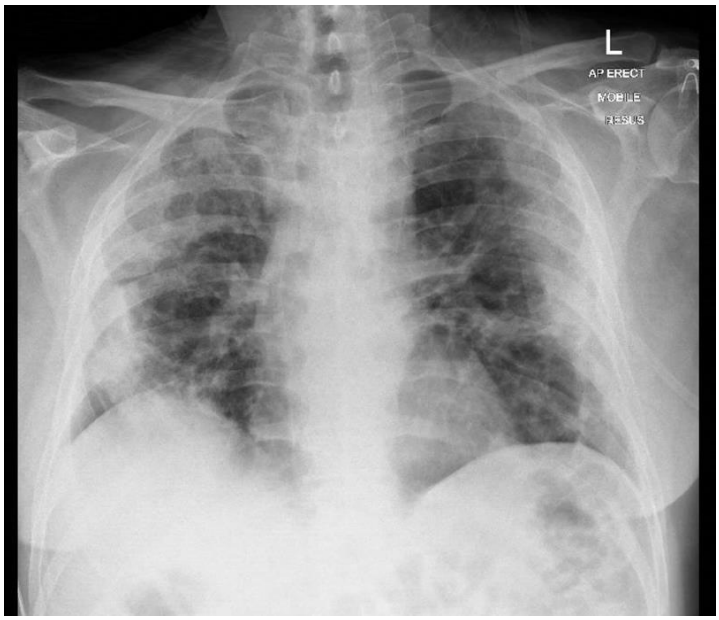
	Patient 1	Patient 2	Patient 3
Demographics			
Age, years	46	62	44
Sex	Male	Male	Male
Ethnicity	Caucasian	Caucasian	Afro-Caribbean
Clinical findings			
Co-morbidities	Morbid obesity Alcohol abuse	Morbid obesity Hypertension	Morbid obesity Hypothyroidism GORD
Concomitant treatment for COVID-19	IV co-amoxiclav Oral clarithromycin Prophylactic dose enoxaparin	IV co-amoxiclav Oral clarithromycin Prophylactic dose tinzaparin, switched to rivaroxaban on diagnosis of pulmonary embolus	IV co-amoxiclav Prophylactic dose tinzaparin
SOFA score on admission	5	6	7
Blood pressure on admission, mmHg	134/90	90/67	122/76
PaO_2 on admission (room air), kPa	8.11	8.44	8.23
O_2 saturation on admission on arterial gas (room air), %	92.7	92.8	92.7
FiO_2 required via Venturi mask, %	40	40	40
CRP on admission, mg/dL (normal range <6)	224	147	209
Imaging findings on admission	Extensive bilateral nodular densities with superimposing consolidation involving both lungs	Peripheral ground glass opacification throughout both lobes	Extensive bilateral peripheral patchy opacification
Day of admission on which iloprost infusion was initiated	2	9	2
PaO_2/FiO_2 pre-iloprost, mmHg	152	158	154
PaO_2/FiO_2 5 days post-iloprost, mmHg	344	312	330
Adverse effects from treatment	None	Diarrhoea	None
Bleeding complications	None	None	None
Disease-related complications	None	Pulmonary embolus	None
Clinical outcome	Discharged on day 8	Discharged on day 22	Discharged on day 7

GORD=Gastro-oesophageal reflux disease. SOFA score=sequential organ failure assessment score.

Supplementary Table: **Demographic and clinical characteristics of three patients with COVID-19 treated with 5-day continuous iloprost infusion.**



Supplementary Figure 1: **Effects of a continuous 5-day infusion of iloprost therapy given to COVID-19 patients with peripheral ischaemia (n=3).** Data are mean values; errors bars indicate standard error of the mean. First arrow indicates when infusion was initiated. Second arrow indicates when infusion was stopped. *=p<0.05, **=p<0.01, compared to baseline values with a paired t-test. PaO_2=partial pressure of oxygen in arterial blood. FiO_2=fractional concentration of oxygen in inspired air. bpm=beats per minute.



Supplementary Figure 2: **Chest radiograph on admission showing bilateral peripheral patchy opacification consistent with COVID-19 (B) from one patient.**