Case Series

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Role of Sildenafil in Severe COVID-19 Pneumonia in Infancy - A Case Series

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Abstract

SARS-CoV-2 virus primarily affects the respiratory system, although other organ systems are also involved. Though pulmonary arterial hypertension (PAH) has been described in as a sequela of COVID pneumonia in adults, only a coincidental association between pre-existing PAH and SARS-CoV-2 infection in children has been reported. To our knowledge, severe COVID pneumonia-causing PAH in children, especially in infancy has not been reported yet. With the meteoric spread of the pandemic and rapid development of newer mutated variants, the timely discovery of new drugs is near impossible. The idea of repurposing existing drugs to treat COVID-19 is an attractive strategy, especially if they are already approved (for other indications) and have well-established safety profiles.

Sildenafil specifically targets pulmonary vasodilation, endothelial function, and vascular remodelling. It hence has emerged as an effective first - line oral therapeutic agent for patients with symptomatic PAH in all age groups. We present a case series of four cases where Sildenafil has been repurposed for the treatment of PAH associated with severe COVID-19 pneumonia in infancy.

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Introduction

The novel human coronavirus disease (COVID - 19) was first reported in Wuhan, China in 2019 and subsequently spread globally to become the fifth documented pandemic since the 1918 flu pandemic.[1] SARS - CoV - 2 virus primarily affects the respiratory system, although other organ systems are also involved. Respiratory symptoms of COVID -19 are extremely heterogeneous, ranging from minimal symptoms to significant hypoxia with ARDS.[2] Even though autopsy studies of adult patients who died of severe SARS - CoV - 2 infection reveal the presence of diffuse alveolar damage consistent with ARDS, a higher thrombus burden in pulmonary capillaries is also seen.[3] The most probable mechanism for refractory hypoxemia in SARS CoV - 2 pneumonia is the involvement of the microcirculation by thrombi, as seen in autopsy reports in adults.[4,5]

With the meteoric spread of the pandemic and rapid development of newer mutated variants, the timely discovery of new drugs is near impossible. Repurposing existing drugs to treat COVID-19 is an attractive strategy, especially if they are already approved (for other indications) and have well- established safety profiles.[6-8] Sildenafil specifically targets pulmonary vasodilation, endothelial function and vascular remodeling. It hence has emerged as an effective first-line oral therapeutic agent for patients with symptomatic PAH in all age groups.[9,10] We present four cases where Sildenafil has been repurposed for the treatment of pulmonary arterial hypertension (PAH) associated with severe COVID-19 pneumonias in infancy.

Case 1

A two - month - old baby girl presented to the emergency with a history of recurrent apnea and respiratory distress. She was born preterm (32 weeks POG) with low birth weight (1.18 kg) and was referred from another hospital with a diagnosis of sepsis, hypoxic-ischemic encephalopathy, anemia and leukopenia. She was on mechanical ventilation for almost one month with failure to extubate on three occasions during her stay in the previous hospital. The COVID-19 RT PCR was positive. She had also tested positive for aspergillosis (Galactomannan test) for which she was on liposomal Amphotericin B for last three weeks in the previous hospital. Chest CT revealed a CORAD score (Table 1)[11] of 5 with a fungal ball on the right side. Serum C- Reactive Protein (CRP), ferritin, D- dimer and lactate dehydrogenase (LDH) levels were elevated (Table 2).

She was continued on mechanical ventilation with FiO_2 of 70% and PEEP of 7 cm. She was given one unit of packed RBC transfusion and started on inj meropenem, inj methylprednisolone, tablet voriconazole and inj levetiracetam along with other supportive care. 2D Echocardiogram revealed PAH (Pulmonary arterial pressure = 32 mm Hg). Tablet sildenafil was started at 2 mg / kg / dose QID. A reduction in oxygen requirement and improvement in respiratory status was noticed within a couple of hours of starting sildenafil and was extubated on day 3. However, fluctuating oxygen requirement remained for the next two days and finally, the infant was weaned off oxygen on day six of admission though radiological clearance took some time. Follow up echo done after two weeks was normal without any evidence of PAH. The baby was discharged with hemodynamic stability and significant weight gain and on expressed breast milk feeds after a hospital stay of one month.

Case 2

A four - month - old baby boy presented with fever and cough for 15 days and respiratory distress for 10 days. He was admitted in another hospital with the above complaints where he had received oxygen therapy, IV antibiotics, and blood transfusion once. He was referred to our hospital in view of worsening respiratory distress. RT PCR for COVID-19 was negative at the previous hospital. On the second day of admission, respiratory distress worsened. The child developed one episode of status epilepticus - and an episode of cardiac arrest. The child was put on mechanical ventilation after adequate resuscitation. The child was given IV antibiotics, anticonvulsants, vasopressor and inj methylprednisolone. Chest CT revealed a CORAD score of 5. Serum CRP, ferritin, D-dimer, and LDH levels were elevated (Table 2). Fever persisted and blood culture showed growth of Klebsiella pneumoniae, while urine culture showed growth of Candida tropicalis though laboratory flagged both the growths as contaminant. Tablet Voriconazole was also started. The child was extubated after three days. Respiratory distress persisted with high oxygen demand. 2D ECHO revealed PAH (Pulmonary arterial pressure = 30 mm Hg). Tablet sildenafil was started at 2 mg / kg / dose QID. A dramatic improvement in respiratory status was noticed within a couple of hours of starting sildenafil. The child was discharged with hemodynamic stability and direct breastfeeding after 21 days of hospital stay with a tapering dose of oral steroids, tablet sildenafil and tablet voriconazole.

Case 3

A two - month - old male infant presented with complaints of fever, cough, and respiratory distress. The baby had been symptomatic since 30 days of life with the above complaints and had been admitted in another hospital. He was referred to our hospital in view of persistent oxygen requirement. Apart from a birth injury to the right upper limb, the birth history was not significant. The baby developed convulsions on the evening of the day of admission. The baby was started on IV fluids, IV antibiotics and anti-epileptics. All the inflammatory markers were elevated (Table 2). COVID -19 IgG titer was positive. High-Resolution Computed Tomography (HRCT) chest was suggestive of obliterate bronchiolitis and 2 D echo revealed the presence of PAH (Pulmonary arterial pressure = 38 mm Hg). Inj methyl prednisolone and tablet sildenafil were started along with other supportive care. There was a decrease in the oxygen demand of the baby. The baby is currently maintaining oxygen saturation with free flow oxygen and on top feeds.

Case 4

A two - month - old baby boy presented with complaints of fever, cough and respiratory distress. He had been admitted in another hospital with the above complaints for three days. The baby was referred to our hospital in view of worsening respiratory distress. A history of delayed / poor cry was present. However, the baby was discharged after two days of hospital stay after birth. The baby developed convulsions on the night of admission. The baby also had tachycardia disproportionate to fever, hepatomegaly, and S3 gallop with a mitral regurgitant murmur which were highly suggestive of myocarditis. He had to be put on mechanical ventilation the following day after multiple episodes of convulsions and deterioration of vitals. The baby was started on IV fluids, IV antibiotics, and anti - epileptics with inotropes and vasopressors. 2D ECHO showed myocarditis with a poor ejection fraction and PAH (Pulmonary arterial pressure = 35 mm Hg). Inj methylprednisolone and intravenous immunoglobulin (IVIg) were started. The baby was extubated after four days of mechanical ventilation. Respiratory distress persisted with a high oxygen demand and had an episode of seizures and decerebrate posturing with desaturation. All the inflammatory markers were elevated (Table 1). COVID -19 IgG titer was positive. Tablet sildenafil was started on day 1 of extubation and within hours, respiratory distress settled and oxygen requirement reduced dramatically. The baby is still on oxygen by nasal prongs at 2 litre / minute and the respiratory rate and work of breathing had reduced significantly.

Discussion

The group of patients in our cohort had similarities in age (Less than six months), clinical features (fever, cough, respiratory distress,

refractory hypoxemia, convulsions), presentation after around two weeks of initial symptoms and unvaccinated COVID-19 status in the mothers and on predominantly top feeds. Temporal association with COVID-19 infection (RT PCR / IgG / HRCT positivity), elevation in acute phase reactants and d-dimer levels, and presence of PAH on 2D ECHO was also present in all the four cases. And all of the cases showed dramatic improvement in respiratory status after the inclusion of tablet sildenafil in therapy. We used sildenafil orally at a dose of 2 mg / kg every 6 hourly for 5 days and then tapered by 0.5 mg / kg / q every 5 days with a total duration of 25 days.

Though PAH has been described in adults as a sequela of COVID pneumonia in adults,[12-14] only a coincidental association between pre-existing PAH and SARS CoV2 infection in children has been reported.[15] To our knowledge, severe COVID Pneumonia causing PAH in children, especially in infancy has not been reported yet. The mechanism of PAH in severe COVID pneumonia is poorly understood. Two possible mechanisms are pulmonary thromboembolism and direct invasion of the pulmonary microcirculation by Novel Coronavirus.[16] These lead to blockage and eventually remodeling of pulmonary vasculature which may result in right ventricular hypertrophy ultimately causing PAH. Sildenafil may have a therapeutic effect by causing pulmonary vasodilatation.

COVID-19 was initially thought to cause only mild symptoms in children. However, our report shows that paediatric population can at times be vulnerable to this frightening complication of COVID-19 pneumonia. Though the number of cases represented in our study is small but finding out a dramatic response to sildenafil in a cohort of patients with similar characteristics mandates further evaluation of the drug in cases of severe SARS- CoV-2 pneumonia. More focused research is required in this direction. And Sildenafil may be a helpful addition in the treatment protocol in addition to steroids in severe respiratory involvement with refractory hypoxemia.

Conclusions

PAH is a common sequelae / complication of severe COVID-19 pneumonia in children which presents with worsening respiratory distress. Sildenafil is a useful drug to existing treatment protocol to tackle this complication of PAH in COVID-19 children. However, the findings of this case series should be evaluated further in elaborate clinical research in the future.

List of Tables

Table 1. Overview of CO-RADS Categories and the Corresponding Level of Suspicion for Pulmonary Involvement in COVID-19

CO-RADS category	Level of Suspicion for Pulmonary Involvement of COVID-19	Summary
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very Low	Normal or noninfection
2	Low	Typical for other Infection but not COVID-19
3	Equivocal/ unsure	Features Compatible with COVID -19 but, also other diseases
4	High	Suspicious for COVID-19
5	Very High	Typical for COVID-19
6	Proven	RT-PCR positive for SARS –CoV-2

Note:- CO-RADS = COVID-19 Reporting and Data System, COVID-19=coronavirus disease 2019, RT- PCR=reverse transcription-polymerase chain reaction, SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.

Table 2. Investigations

Parameter	Case 1	Case 2	Case 3	Case 4
Ferritin (ng/ml)	>1200	968	639.5	250
d-dimer (ng/ml)	>10000	1470	1329	>5000
CRP (mg/dl)	12.21	104.8	38	20.89
LDH (IU/L)	1485	791	362	312
Temporal association with COVID 19	RTPCR positive. CORAD 5 on HRCT chest	CORAD 5 on HRCT chest COVID IgG positive	COVID IgG positive	COVID IgG positive
Others	Galactomanan positive (Asperigellosis)	Klebsiella pneumonia on blood C/S, Candida tropicalis growth in urine C/S		

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