CASE REPORT

Extracorporeal membrane oxygenation for post-transplant hypoxaemia following very severe hepatopulmonary syndrome

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SUMMARY

Hepatopulmonary syndrome (HPS) associated with end-stage liver disease has a high morbidity when room air PaO₂ is less than 50 mm Hg. Safe levels of oxygenation to facilitate transplantation have not been defined despite advancement in care. Postoperatively, hypoxaemia worsens due to ventilation perfusion mismatch contributed by postoperative pulmonary vasoconstriction and due to decrease in endogenous nitric oxide. A 16-year-old boy with cirrhosis presented with HPS and a PaO₂ of 37 mm Hg on room air and underwent living donor liver transplant. Although stable intraoperatively, he desaturated on the second postoperative day. Despite a number of interventions, oxygenation remained critically low on 100% inspired oxygen. Extracorporeal membrane oxygenator (ECMO) was established with instant improvement in oxygenation (PaO₂ 68 mm Hg), and the patient was eventually salvaged. We suggest that ECMO could be a means of managing refractory post-transplant hypoxaemia in patients with HPS.

BACKGROUND

Hepatopulmonary syndrome (HPS) is associated with end-stage liver disease with potential for reversibility after liver transplant. Dilated pulmonary arteriovenous channels lead to mismatch in ventilation and perfusion with progressive hypoxaemia. The triad of HPS involves portal hypertension with or without cirrhosis, hypoxaemia and elevated alveolar to arterial oxygen gradient.^{1 2} Although the treatment for established HPS is liver transplant, severe hypoxaemia with PaO₂ less than 50 mm Hg has been associated with high postoperative morbidity.³ We report the case of postoperative hypoxaemia due to very severe HPS following liver transplant complicated by diabetes insipidus (DI) that was successfully managed with extracorporeal membrane oxygenator (ECMO) and supportive care.

CASE PRESENTATION

A 16-year-old boy presented to the hospital for the management of increasing breathlessness. He had been diagnosed with chronic liver disease, non-alcoholic steatohepatitis with significant hypoxaemia (figure 1). He had undergone a resection of craniopharyngioma at 7 years of age and was on hormone replacement with levothyroxine, steroid and intermittently on testosterone after surgery.

He was not on vasopressin replacement therapy, and electrolytes were normal (serum sodium 138 mEq/L). His dyspnoea had increased progressively, and at the time of presentation, he was on home oxygen at 2 L at night. His room air saturation was SpO₂ 68% and PaO₂ 37 mm Hg that fitted a grading of very severe HPS⁴ (table 1).

INVESTIGATIONS

Transthoracic echocardiography revealed normal pulmonary artery pressures, and a contrast echocardiography showed air bubbles in the left heart after five to six cardiac cycles. A CT image of his chest with contrast showed no discrete pulmonary arteriovenous channels. Technetium macrolabelled albumin aggregate scan showed an uptake of 17% by the brain quantifying the degree of intrapulmonary shunting.

DIFFERENTIAL DIAGNOSIS

The preoperative signs and symptoms and investigations seemed to suggest a pulmonary vascular dilatation in the background of cirrhosis with portal hypertension. Transthoracic echocardiography with agitated saline ruled out the presence of intracardiac shunts. Distinct pulmonary arteriovenous malformations amenable to coil embolisation were absent.

TREATMENT

HPS is potentially reversible following liver transplant, and the patient was offered surgery with his mother volunteering as a right lobe donor. Oxygenation improved under anaesthesia, although an arrangement for nitric oxide was kept ready. The patient underwent an uneventful surgery that lasted 8 hours and was managed in the postsurgical intensive care unit (ICU). After a relook laparotomy for a bleed on first postoperative day (POD1), he was extubated on POD2 with stable haemodynamics and PaO₂ of 87 mm Hg (FiO₂ 0.5). Four hours later, he started to desaturate, and his blood gases showed a PaO₂ 36.9 mm Hg and SpO₂ 67% on a rebreathing mask. He showed significant diuresis at 350 mL/h, and serum sodium had risen to 189 mEq/L from 148 mEq/L. Vasopressin was reinstituted on a diagnosis of DI, and the patient was intubated with an aim of restoring oxygenation.

Bedside echocardiography revealed minimal increase in right ventricular systolic pressures but

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Figure 1 Clubbing with cyanosis.

Figure 2 Venovenous extracorporeal membrane oxygenation.

good biventricular function. This excluded a primary myocardial dysfunction or pulmonary artery hypertension that could have contributed to his oxygenation failure postoperatively. We did not repeat a bubble echocardiography to assess intrapulmonary shunting following surgery. His oxygenation status improved with volume-controlled ventilation targeting tidal volume of 450 mL achieving peak pressures of 24 mm Hg. However, the oxygenation progressively decreased despite normal lung compliance. The normal lung compliance and absence of significant X-ray findings excluded a pulmonary cause for his respiratory failure. However, an elective tracheostomy was performed on POD5 in anticipation of prolonged ventilation.

On POD6, saturation decreased to 39%–40% (PaO_2 49 mm Hg) despite pressure controlled, inverse ratio ventilation at 100% FiO_2 . Cardiac status and lung investigations were unremarkable, but the bronchoalveolar lavage grew *Staphylococcus haemolyticus* sensitive to linezolid that was instituted for treatment. Ventilatory strategies or Trendelenburg position did not improve the oxygenation. As the X-ray and echocardiography did not appear to indicate infiltrates suggestive of respiratory distress syndrome or cardiogenic pulmonary oedema, the presumptive diagnosis was worsening HPS. Other than modulation of ventilatory strategies and head down position, prone positioning was not considered. Vasodilatory strategies including inhaled nitric oxide, intravenous prostacyclin and inhaled prostaglandin^{4 5} were considered, but none of these were available to us at this time. Intravenous methylene blue is reportedly useful by its inhibition

of nitric oxide synthase effect and inhibition of pulmonary angiogenesis⁶ but was not available to us. The oxygenation decreased further, and for want of other measures, a salvage ECMO was considered as a life-saving measure. ECMO was established with a venovenous circuit from the right internal jugular and femoral vein and position of the cannula confirmed by transthoracic echocardiography (figure 2). The blood gases instantly improved to PaO_2 of 68 mm Hg at pump flows of 3.8 L and FiO_2 between 70% and 80% and sweep gas flow rates of 2–3.5 L. During the next 10 days, this was reduced to 35%–40% FiO_2 and 0.6–1.0 L flow rate. On the 13th day of ECMO, he was weaned over to volume-controlled ventilation. The patient was weaned off from the ventilator 3 days later and continued to receive intermittent continuous positive airway pressure (CPAP) and oxygen through the tracheostomy.

OUTCOME AND FOLLOW-UP

During this period, he received treatment for chest infection and vasopressin for DI, and nutrition was maintained with Ryle's tube feeds. He also received 4 U of packed red cells, 2 U of apheresis platelets and 2 U of random donor platelets. At the time of weaning from ECMO, he was saturating 73% on 50% oxygen on volume-controlled ventilation. We are uncertain of definite oxygenation levels for weaning from ECMO in patients with established hypoxaemia and did not expect significant improvements in oxygenation following transplant until 3 months after surgery. We accepted these levels as they matched

Table 1 Blood gas profile

	Baseline	Start of surgery	At extubation	After extubation	Day 6	On ECMO	Day 13 post-ECMO
pH	7.44	7.39	7.41	7.38	7.21	7.52	7.47
PCO_2	30.8	32	45.7	42.4	46.9	27.4	30.9
PO_2	37.3	286	84.2	36.9	25.9	60	40.3
HCO_3	22.3	21.5	28.4	24.8	16.8	22.5	23.6
SpO_2	67.9	99	96.8	67.1	*	92	72.6
Na	137	144	157	189	134	147	138
Cl	97	116	132	142	89	110	103
K	3.4	3.6	3.4	2.9	2.4	4.6	3.4
FiO_2	0.21	1	0.5	1	1	1	0.5

*Not recordable.

Values in bold indicate baseline saturation on room air and serial values perioperatively ECMO, extracorporeal membrane oxygenation.

his preoperative oxygenation status, and the patient appeared to be comfortable clinically. His DI had settled on maintenance doses of vasopressin 6–8 subcutaneously. He was weaned off the ventilator on the third day after ECMO support withdrawal. He, however, needed intermittent CPAP to maintain saturation in the range of 80%. His ICU stay was complicated by chest infection, wound infection with fever managed with antibiotics and wound debridement in the ICU. He was shifted to the ward on the POD37, and tracheostomy decannulated on the POD38. At the time of discharge, he was maintaining a room air saturation of 80%–83% that dropped to 70% while ambulating. Domiciliary oxygen treatment was not offered, as the patient remained comfortable.

DISCUSSION

Reports from the United Network of Organ Sharing (UNOS) database have shown that a resting PaO_2 less than 44 mm Hg is a predictor of increasing mortality⁷; however, the threshold for deferring surgery is undefined. Our patient had a room air PaO_2 of 37 mm Hg with an alveolar to arterial gradient of 75 mm Hg. Similar to other studies,^{8–10} our patient developed desaturation following extubation that was managed with ECMO. Monsel *et al*¹¹ have described ECMO as a bridge to successful orthotopic liver transplant (OLT) in a patient with adult respiratory distress syndrome (ARDS) associated with chronic liver disease (CLD). Infection of the chest appeared to have contributed to the desaturation in addition to postoperative pulmonary vasoconstriction of normal vessels. Nitric oxide is useful in the management of hypoxaemia associated with HPS.¹² A proposed mechanism is the abrupt alteration of substances mediating pulmonary vasodilatation following liver transplant and benefit of vasodilatation induced by nitric oxide.³ However, nitric oxide was not available to us, and in the context of life-threatening hypoxaemia, ECMO became an available option. Although it is possible that the introduction of nitric oxide could have improved oxygenation at the time of critical hypoxaemia, reports are inconsistent on the successful use of nitric oxide in HPS.^{3 12} Methylene blue is a potent vasoconstrictor that acts by inhibition of cyclic guanosine monophosphate. A single report in a non-transplant setting of seven patients showed improvement.¹³ The mechanism is vasoconstriction in the dilated pulmonary vessels in the lower lung zones and redirection of blood to the upper and middle lung zones.⁵ Although it has been suggested that methylene blue can be administered with the patient in head-up position and combined with a inhaled vasodilator, reports of its successful use are unavailable. We did have concerns regarding the use of ECMO in a post-transplant patient. Despite the use of a heparin-bonded circuit, we had infused heparin targeting an activated clotting time between 180 and 200 as per practices in most centres.¹⁴ There was a possibility of bleed, and platelets were transfused during ECMO therapy. Auzinger *et al* have reported avoidance of heparin or anticoagulation for up to 3 weeks on ECMO. However, we feel that heparin usage appears justifiable in the absence of ongoing bleed.⁹ It is probable that the low model for end stage liver disease (MELD) and good graft function were protective from excessive bleeding in our patient. Our use of two venous cannulae, one in the superior vena cava (SVC) and the other through the femoral vein, added increased risks of infection and bleed. The Wang-Zwische double-lumen cannula reported by the same authors would have minimised the need for two access sites and may have supported

earlier weaning.⁹ Our patient had experienced post-transplant hypoxaemia, which is associated with 45% mortality in those with preoperative $\text{PaO}_2 < 70$ mm Hg.⁴ ECMO use contributed to survival in our patient, although the availability of other modalities including nitric oxide earlier may have changed the clinical management.

Learning points

- ▶ Hepatopulmonary syndrome is a treatable oxygenation disorder in chronic liver disease.
- ▶ Extracorporeal membrane oxygenation is a useful modality for the management of refractory hypoxaemia and may improve the scope for surgery in hepatopulmonary syndrome.

Contributors LK clinically associated, researched and wrote the manuscript. DB clinically involved and contributed to the successful management of the case. RV assisted in patient management and reviewed manuscript. SS supervised and was involved in case management and contributed to the writing of manuscript.

Competing interests None declared.

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