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Management of Acute Respiratory Distress Syndrome: A Challenge to Modern Medicine

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is an acute inflammatory pulmonary injury in which marked oedema of the lungs causing progressive impairment of gas exchange, atelectasis, and decreased lung compliance. Over the years, several innovative methods to control the lung injury had been studied. Improvement in ventilation strategy has resulted in reduce mortality is ARDS patients. Meanwhile, adjunctive therapies such as inhaled nitric oxide, exogenous surfactant administration, patient positioning and immune-nutrition are other methods which may further improve the outcome of this condition. This case illustrates the use of multiple modalities of treatment which were useful in infant with this condition and a review of these treatment modalities.

Keywords: ARDS; Lung injury; Nitric oxide, Surfactants; Immuno-nutrition

Case Illustration

A 4-month old boy (corrected age 1/1/2 month old) was brought to the casualty in a collapsed state after being found cyanosed at home. He was born premature at 29 weeks of gestation with birth weight of 1.3 Kilograms (Kg). He was ventilated for 3 days after birth and was discharged well at day 40 with a weight of 2.1 Kg. He was not on any medications. He had cough and fever for a week. Two days before this presentation, he had one brief episode of cyanosis after bouts of coughing. He was treated for simple upper respiratory tract infection by a general practitioner. He appeared lethargic and feeding poorly on the day of presentation. He was found to be cyanosed and ceased breathing by the babysitter and thus brought to the casualty.

At the casualty he was noted to be bradycardic and apneic. He was immediately intubated, and resuscitated with IV adrenaline, cardiac compression and fluid boluses. After stabilization, he was transferred to the Paediatric Intensive care unit for further management. He required high ventilator support on conventional ventilator. He was tachycardiac, poorly perfused, hypotensive with severe metabolic acidosis. There were generalized crepitations of the lungs and hepatomegaly. The chest X-ray showed patchy opacities of both lungs. He was treated for severe pneumonia with sepsis. Intravenous Cefotaxime was started. The metabolic acidosis gradually improved with fluid correction and sodium bicarbonate infusion. He was hypotensive and required dual inotropic support. He also had an episode of seizure which was terminated by intravenous phenobarbitone.

On the next day, he developed persistent desaturation. High Frequency Oscillatory Ventilation (HFVO) was initiated and followed by inhaled nitric oxide. The oxygen saturation improved to 95% but the oxygen index was high. He also had hypercapnia despite being on HFOV setting. He developed oliguria and started on intravenous frusemide infusion. He also had coagulopathy with thrombocytopenia requiring platelet concentrate and plasma transfusion. Antibiotic was changed to intravenous Meropenem on day 4 of admission. The blood culture however did not grow any bacteria. Viral serology and screening for respiratory viruses were also negative. He remained unstable and developed persistent hypoxaemia. The oxygenation furthers deteriorated to 60-70% on day 6. The repeat chest X-ray showed diffuse lung opacity consistent with the diagnosis of Acute Respiratory Distress Syndrome (ARDS). A decision was made for trial of surfactant. Pure Survanta, 4 ml/Kg body weight was instilled through the endotracheal tube while the patient was turned into various positions, supine-right lateral- supine- left lateral. Prone position was not attempted as the patient had severe desaturation and bradycardia when nursed in this position. During the initial instillation of surfactant, the patient desaturated to 35% and was bradycardic to 90 beats per minute which improved with ambubagging. Transient improvement of oxygenation was observed with surfactant administration. However, the patient further desaturated with oxygen saturation around 50% to 70% throughout the night. The parents were informed of the poor prognosis.

Unexpectedly, the oxygen saturation slowly improved to 80-85% by the next morning. The partial pressures of oxygen also improved from 23 mmHg to 51 mmHg. He became more stable two days later; the oxygen saturation gradually increased to above 93% without any changes made on the ventilation setting. As oxygenation improved and above 95%, inhaled nitric oxide and FiO_2 were slowly weaned down. The patient also started to move the limbs and opened the eyes. Over the next few days, the liver and renal impairments became normalized. Inotropic support was able to be weaned off.

After 2 weeks, he was extubated to nasal CPAP. He required nasal oxygenation supplied for about 1 month until he was discharged after 38 days with MDI inflammide and ventolin. He required sucking stimulation therapy but able to feed from bottle 2 months later. He was last seen at 61/2 months of corrected age. By then his developmental milestone was appropriate for the age.

Discussion

Acute Respiratory Distress Syndrome (ARDS) was first described in 1967 in 12 adult patients. It was then addressed as Acute Hypoxaemic Respiratory Failure [1]. The American-European Consensus Conference on ARDS (1994) introduced the first definition of ARDS and another benign form of acute respiratory failure termed Acute Lung Injury (ALI). ARDS and ALI are defined as respiratory illnesses with an acute onset with the presence of bilateral infiltrates on chest radiography and a documented pulmonary artery wedge pressure = 18 mmHg (or absence of clinical evidence of left atrial hypertension). In ALI, the PaO_2/ FiO_2 ratio is = 300. In ARDS the PaO_2/ FiO_2 ration is = 200 [2]. Nonetheless, over the past 20 years, the diagnostic accuracy of this definition has been questioned. Thus the revised definition was recommended by the ARDS definition task force which formulated the "Berlin Definition" in 2012. In this definition, ALI has been omitted with ARDS being categorized into 3 mutually exclusive categories based on the degree of hypoxemia [3].

The incidence of ARDS is between 15 to 75 persons per 100,000 [4]. The true incidence of ARDS in general population however is difficult to be estimated as the disease is heterogenous. ARDS may result from variety of insults to the lung, either directly or indirectly through a systematic process. The mortality rate associated with ARDS in adults was greater than 50% until recent years when outcomes seemed to improve, possibly due to improvement in the medical advances. Review of the pediatric literature suggests similar trend, with reported mortality rates as low as 10% to 30% [4]. Most deaths in adult and pediatric ARDS patients are attributed to sepsis or multiorgan failure. However, ventilation strategies that presumably minimize ventilator induced lung injury (VILI) have been shown to reduce mortality, suggesting that lung injury may be indirectly related to death in ARDS.

Mechanical ventilation increases the risk of VILI through two potential mechanisms; over-distension of gas-filled alveoli and the repetitive opening and closing of atelectatic alveoli. The risk is higher in ARDS because normal and diseased lung tissues are interspersed. In addition, inappropriate ventilation may initiate an inflammatory cascade causing further damage to the surfactant system and worsening of pulmonary oedema [1]. The results from the ARDS network study in 2000 have changed the ventilator management of ARDS and ALI. The use of tidal volume of 6 ml/Kg and limiting plateau pressures to less than 30 cm H_2O had improved clinical outcome in adults when compared with traditional tidal volumes of 12 ml/Kg and plateau pressure of less than 50 cm H_2O. The low tidal volume group showed a 22% reduction in mortality, increased ventilator-free days and fewer hospital days with extrapulmonary organ failure [5]. Other modes of ventilation such as High-Frequency Oscillatory Ventilation (HFOV), Airway Pressure Release Ventilation (APRV) and Partial Liquid Ventilation (PLV) are being evaluated while following this ventilation strategy.

Our patient had been managed with HFOV which is available at our unit. HFOV reflects the extreme form of reduced tidal volume delivery, providing 1-2 ml/Kg inspiratory volumes at frequencies of 6 to 15 Hz. The mean airway pressure is set to maximize lung expansion and oxygenation, while the power is set to determine the amplitude of oscillations, which control ventilation. In our practice, HFOV is used as a rescue therapy as shown in the case above. If patients appear to require high tidal volumes or peak inspiratory pressures, they are given a trial of HFOV. The use of HFOV has been shown to be safe and effective as a rescue mode in improving oxygenation in children with ARDS. Fedora et al. (2000) found a significant difference in mortality, 58.8% survival in patients placed on HFOV within 24 hours compared to 12.5% in patients placed on HFOV beyond 24 hours [6]. Although this study was relatively small, it appears that early initiation of HFOV in pediatric respiratory failure is associated with better oxygenation and consequently, a better outcome.

Apart from mechanical ventilation strategy, the introduction of pulmonary vasodilator agent such as inhaled Nitric Oxide (iNO), have attracted researchers to evaluate its effectiveness in ARDS. It is a free radical gas released by the endothelial cells in the lung. It causes pulmonary vasodilatation via the secondary messenger cyclic guanosine monophosphate. It decreases ventilation-perfusion mismatch by selectively vasodilate blood vessels at the well-ventilated alveoli. It has also been shown to regulate immune and inflammatory responses as well as decreases the oedema formation. Rossaint et al. first demonstrated in adult ARDS patients that iNO decreases intrapulmonary shunting and improves arterial oxygenation [7]. Abman et al. (1994) had described beneficial effects of iNO on oxygenation, pulmonary hypertension and cardiac index in children with ARDS [8]. Subsequent studies then have shown similar effects but unable to show sustained response in this therapy [9]. In 2002, the Cochrane Library review concluded that the iNO may be useful only as a rescue treatment in the first 24 hours of the disease. Although it has been shown to improve oxygenation in ARDS, it is not found to increase survival rate or the number of ventilator-free days [10]. Our patient was started on inhaled nitric oxide (iNO) at 30 hours of admission. He showed slight improvement in oxygenation but deteriorated again after 4 days of HFOV and nitric oxide.

Surfactant was administered in our patient as a last effort to salvage the lung injury. Exogenous surfactant administration has a proven benefit in the treatment and prevention of neonatal respiratory distress syndrome (RDS). However, its value in treating ARDS has not been established. The rationale for the use of exogenous surfactant is based on the observation that the condition causes overall lack of surfactant function. This contributes to atelectasis, shunt, and gas-exchange abnormalities and may predispose such patients to pulmonary infection. The administration of exogenous surfactant in ARDS population has been shown to be feasible and safe. Moller et al. (2003) reported that bovine surfactant 100 mg/Kg body weight administered intra- tracheally improved oxygenation immediately after administration, but the study was limited by its small sample size [11]. A number of different types of exogenous surfactant have been tested in clinical trials. Animal-derived surfactant products have been more effective than synthetic surfactant because of the risk of transmitting infectious agents. Wilson et al. conducted a multicenter, randomised trial of a calf lung surfactant extract, calfactant, on 42 children with ARDS [12]. The study showed that surfactant appears to be safe and caused rapid and sustained improvement in oxygenation. The group that received surfactant spent significantly less time on mechanical ventilator and shorter ICU stay compared to the control group. However, there were no differences in mortality. Similarly, Spragg et al. [13] found improve oxygenation after administration of recombinant surfactant protein C-based surfactant in adults with ARDS; however did not show increase survival. The use of surfactant is costly especially in adult population. Its use in pediatric-aged patients has been shown to be cost-effective. This could be due to the smaller amount need to be used in children as well as cost saving from a shorter PICU stay [14]. In our patient, we had used intra-tracheal instillation of Survanta 4ml/Kg body weight. There was initial improvement of oxygenation after the surfactant administration which only sustained for a brief period. The actual improvement in

oxygenation was only seen two days later which made it difficult for us to relate this to the effect of this treatment. The patient also had multi-organ failure which had shown improvement during this time thus the improvement in oxygenation may well be effect of the recovery phase in the disease process itself rather than the effect of the treatment per se.

Other method that was previously studied in the non-ventilation management of ARDS is prone positioning which was also attempted in our patient. Prone position was suggested to be a maneuver that can improve ventilation-perfusion matching in patients with severe impairment of gas exchange. There is however no data that suggests improved clinical outcomes. Curley et al. examined prolonged periods of prone ventilation combined with a lower tidal volume approach in children aged 2 weeks to 18 years with ARDS. They were not able to demonstrate beneficial effects on clinical outcomes using this method [15]. The prone positioning therefore is not of significant value and thus should not be a routine practice. Although it has been attempted in our patient, it caused further desaturation and thus was discontinued.

Other method of ventilation that is not available in our centre is Extracorporeal Membrane Oxygenation (ECMO), which has been shown to be effective as a rescue therapy [16]. Pharmacological treatment such as corticosteroid has also been shown to be effective in late stage of ARDS by reducing the mediators for fibrosis development. The use of special nutrition that is called immune-nutrition that is believed to help in reducing lung inflammation and improving oxygenation is still in ongoing trials [1].

As a conclusion, the only clinically proven method that can alter the survival of patients with ARDS is the use of low tidal volume strategy. The adjunctive therapies although as attractive as they may appear, remained controversial and need evaluation in larger clinical trials. Whether any single modality used in the treatment of ARDS has a significant effect on overall mortality remained to be explored.

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