Methylprednisolone Therapy in a Child with Unresolving ARDS

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We report successful use of methyl-prednisolone in a 21-month old child with ARDS that did not improve with conventional therapy. The child improved and could be extubated after 10 days of methyl-prednisolone therapy. Subsequently, the child was weaned off supplementary oxygen. Methylprednisolone appeared to be safe and effective in a child with unresolving ARDS.

Key words: *ARDS, Methylprednisolone.*

Acute Respiratory Distress Syndrome (ARDS) causes significant morbidity and mortality in children in intensive care units throughout the world(1). Irrespective of the underlying initiating cause of ARDS, there is loss of integrity of endothelial cells and damage to Type II pneumocytes which sets into motion an inflammatory cascade that result in extensive damage to lung parenchyma. The initial exudative phase is followed by proliferative phase, which leads to organization of exudates, proliferation of type II pneumocytes, and finally the fibrotic phase occurs by day 10(2). At this stage, steroids may help to check the unabated inflammation in lung tissue and have been used in adults with unresolving ARDS once infection is controlled, with good results(3). There is very limited data regarding its use in children with unresolving ARDS(4,5). We report a case of unresolving ARDS in a 21-month-old child who showed marked improvement with methylprednisolone therapy.

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Case Report

A 21-month-old severely malnourished child weighing 7 kg was admitted with chronic diarrhea. Intestinal biopsy showed eosinophilic gastroenteritis and he failed to gain weight on nutritional management of chronic diarrhea(6), so total parenteral nutrition (TPN) was started. About 4 weeks after starting TPN, he had sudden onset of respiratory distress, which was preceded by an accidental bolus of 5 mL of intralipid infusion via his subclavian venous catheter. The patient had increasing respiratory distress requiring intubation and mechanical ventilation. His tachycardia responded to fluid boluses, and his colour and saturation improved after intubation, Peripheral pulses were of good volume and there were no skin petechiae and no electrolyte abnormalities or hypocalcemia. The child had no bleeding manifestations or thrombocytopenia throughout the course. The possibility of fat embolism was considered initially but no supportive evidence for the same was found subsequently.

The chest *X*-ray at the time of admission to the Pediatric Intensive Care Unit (PICU) showed bilateral diffuse infiltrates. The central venous pressure (CVP) was 7 cm H_2O and an echocardiography ruled out any underlying cardiac dysfunction. The PaO_2/FiO_2 ratio was 120, the initial $PaCO_2$ was 57.2 mm Hg. The child was ventilated using Siemens Servo 300 ventilator using pressure regulated volume control (PRVC) mode. The initial ventilator

settings were: tidal volume 60 mL, PEEP 10 cm H_2O, frequency of 30/min and FiO_2 of 100% and 1:E = 1:2 (Ti = 0.7 second). A diagnosis of ARDS was considered. The child received intravenous (IV) antibiotics (Vancomycin, Pipercillin + Tazobactam and Amikacin) and antifungals (Amphotericin B, started prior to this event in view of urinary Candida infection initially). Serial arterial blood gases were done to optimize ventilatory management.

The patient continued to require high settings (PEEP 12 cm H_2O, FiO_2 >60%) without any improvement in clinical condition and the chest *X*-ray showed progressive worsening with a complete whiteout. Cultures (bacterial and fungal) from blood, urine and non-bronchoscopic bronchoalveolar lavage (BAL) fluid, which were done twice weekly, were repeatedly sterile. Cytopathology of BAL fluid showed some neutrophils. After 10 days of positive pressure ventilation and progressively worsening lung picture with no evidence of infection, a possibility of unresolving ARDS was considered and and a decision to administer methylprednisolone was taken, as per the protocol given by Meduri, *et al.*(3): Loading dose of 2 mg/kg, then 2 mg/kg/day from day 1-14; 1 mg/kg/day from day 15-21: 0.5 mg/kg/day from day 22-28; 0.25 mg/kg/day on days 29 and 30 and finally 0.125 mg/kg on days 31 and 32. The PaO_2/FiO_2 ratio at this time was 120 and the PEEP was 12 cm H_2O. Written informed consent from the parents was obtained prior to initiating therapy.

The patient showed improvement, thereafter, in chest findings along with recuction in PEEP to 5 cm H_2O by day 4 of starting methylprednisolone and gradual decrease in FiO_2 requirements. PaO_2/FiO_2 ratio improved to 314 by day 4 and by day 8, the child was stable at PEEP of 5 cm H_2O and FiO_2 of 30%. The chest *X*-ray also showed clearing of the diffuse infiltrates and the patient was finally extubated after 10 days of methylprednisolone therapy. The child maintained normal saturations on oxygen by head box and was then gradually weaned off oxygen and shifted to the inpatient ward, where he received further treatment. No infectious complications, hyperglycemia, hypertension or muscle weakness occurred in the child.

The Institute Ethics Committee waived off the need for informed consent for reporting this case.

Discussion

We successfully used steroid therapy in a young child with unresolving ARDS. We could wean off ventilation a patient who was not responding to all supportive care including high ventilatory support over 10 days. There are trials of methylprednisolone in unresolving ARDS in adults but pediatric data is limited to case reports(4,5).

In unresolving ARDS, the failure to suppress the sustained systemic inflammatory response could be due to inadequacy of and/or tissue resistance to the endogenous glucocorticoids. Of the two cellular signaling pathways -the stimulatory nuclear factor κB (NF-κB) and the inhibitory Glucocorticoid Receptor-α(GR-α) mediated responses - there is increase in GR-α and suppression of NF-κB mediated responses with use of steroids. In addition, levels of cytokines, ACTH and cortisol showed significant reductions(7) and the serial measurement of plasma and BAL Procollagen Type I and III amino terminal propeptides (which reflect collagen synthesis)(8) suggests that steroid therapy reduces fibrogenesis and the chronic lung changes in unresolving ARDS.

Meduri, *et al.* reported use of steroid

therapy in adults with unresolving ARDS who failed to show improvement in lung injury scores (LIS) by day 7(3), with improvement in lung function and mortality as primary outcomes and improvement in MODS score and rate of development of nosocomial infections as the secondary outcomes. The study showed reduced LIS, improved PaO_2/FIO_2, decreased MODS score, and successful extubation in treatment group and rate of infections/day of treatment was similar, with pneumonia being frequently detected in the absence of fever by regular bronchoscopy and assessment of BAL fluid.

There is limited pediatric data, In a case series, the authors used initial short course high dose therapy (30 mg/kg) for 3-6 days, starting from day 4-31 after onset of ARDS in 6 children(4). There is also a single case report from Malaysia in which methylprednisolone therapy was used in a child with unresolving ARDS after 12 days of mechanical ventilation(5).

The following pre-conditions should be met before starting steroids in a patient with unresolving ARDS(3): (*i*) The patient must have no demonstrable infection; (*ii*) Steroids should not be started <7 days or >28 days, from admission; (*iii*) There should be no history of gastric ulceration or active gastrointestinal bleeding; (*iv*) Patients with burns requiring skin grafting, AIDS, and those in whom life support is expected to be withdrawn, are unsuitable; (*v*) The patient should have evidence of ALI and require FiO_2 >50%; (*vi*) Screening for LRTI, by performing protected lavage every 3 to 4 days (while the patient is ventilated), and line sepsis.

To conclude, steroid therapy may have a role in the treatment of unresolving ARDS, provided infection is well controlled. The review of the available literature regarding its use in children highlights the limited experience. Further studies are required to define the optimal time of starting therapy, its duration and doses in children with unresolving ARDS.

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Neonatal Diabetes Mellitus

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Neonatal diabetes mellitus is a rare form of insulin dependent diabetes mellitus that present within the first month of life, lasting at least two weeks and requiring insulin therapy. Intrauterine growth restriction, failure to thrive, fever, dehydration, hyperglycemia and acidosis with or without ketonuria are the clinical features of the disease. We report four cases of neonatal diabetes mellitus; two of them had a transient course.

Key words: *Insulin, Neonatal Diabetes mellitus.*

Impaired glucose tolerance in neonates can be due to various factors including neonatal diabetes mellitus (NDM). Neonatal diabetes mellitus is a rare form of insulin dependent diabetes mellitus (IDDM) with an incidence of 1/400 000 that present within the first four weeks of life persisting for at least two weeks and requiring insulin treatment(1,2). The outcome is highly variable; may be either permanent, or transient with/without subsequent recurrence(3). We present four cases of neonatal diabetes mellitus; two of them had a transient course.

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Case Reports

Case 1

This term male neonate was the fourth child of non-consanguinous parents. The mother was 38 years old and pregnancy was complicated by severe oligohydramnios. His birth weight was 1860 g (<10th percentile) and length was 32 cm (10-25th percentile). The physical examination was normal. His brother had been diagnosed as IDDM when he was five years old.

On the 10th day of hospitalization, he had hyperglycemia (307 mg/dL) and was treated with subcutaneous crystalline insulin because of persistent high glucose levels. He was fed eight times a day with 120 kcal/kg/day. During hospitalization, he sometimes developed metabolic acidosis without ketosis requiring bicarbonate therapy. On the 26th day, subcutaneous isophane (NPH) insulin was started once daily. His insulin and C-peptide levels were 2.2 micCIU/mL (normal values 2.1-30.8 micIU/mL) and 0.2 ng/mL (normal values 1.1-3.2 ng/mL) respectively. Tests for intrauterine infections (TORCH) and islet cell antibodies were negative. He gained 30-50 g/kg/day of weight during hospitalization. On 44th day of hospitalization he was discharged on twice daily insulin regimen. However, his parents gave up insulin treatment after discharge and on follow up at 3 months of age