CASE REPORT

Magnesium sulphate as primary intervention for persistent pulmonary hypertension of the newborns at limited settings in West Papua, Indonesia: A case report

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SUMMARY

Persistent pulmonary hypertension of the newborn (PPHN) is characterised by sustained elevation of pulmonary vascular resistance (PVR), leading to right to left shunting across foetal circulatory pathways. It is one of the main causes of neonatal mortality. There have been studies suggesting standard and advanced managements of PPHN. However, many developing countries do not have access to some of those therapies. Magnesium sulphate (MgSO4), a potent vasodilator, has the potential to reduce high pulmonary arterial pressures. Due to its unspecific action site, its usage in PPHN is still uncommon. We reported a case of PPHN that was managed using MgSO4 in a limited setting district hospital in West Papua, Indonesia. Patient was a normal weight, term baby boy, delivered spontaneously with risk factors of prolonged labour and meconium stained-amniotic fluid (MSAF). Respiratory distress was found shortly after birth with >10% difference of pre- and post-ductal sites. Hyperoxia test was positive. Following his diagnosis of PPHN, he was given oxygen therapy and first-line antibiotics. Standard medications to lower the PVR were unavailable in our setting, so we could only give continuous MgSO4. On the 5th day, improvement was seen in respiratory distress and MgSO4 was stopped. The baby was discharged with a total of 11 days of stay after successfully weaning from oxygen therapy. In this report, we would like to highlight the usage of MgSO4 as an alternative treatment to lower PVR at limited healthcare facilities and haemodynamic monitoring for hypotension and bradycardia that should be conducted.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a condition characterised by sustained elevation of pulmonary vascular resistance (PVR) and is frequently associated with normal or low systemic vascular resistance (SVR), resulting in right to left extrapulmonary shunting across foetal circulatory pathways (patent ductus arteriosus, PDA, and patent foramen ovale, PFO).[1] It prevents the increase in pulmonary blood flow (PBF), which is essential for extrauterine oxygenation and survival, leading to severe hypoxemia which may not respond to conventional respiratory support.[1,2] The incidence of PPHN is 1.8 2/1,000 live births.[2] Despite the availability of advanced neonatal care, PPHN remains one of the major causes of neonatal morbidity and mortality with poor prognosis. The mortality rate is 4 to 33%.[2]

There have been several neonatal cardiorespiratory studies that provided us with better understanding about the pathophysiology and management of PPHN. The management of PPHN, including supportive care and pharmacotherapy to reduce PVR, has been practiced all around the world. Pharmacotherapy's administration routes for pulmonary vasodilators consist of oral, intravenous, and inhalation such as nitric oxide and prostacyclin analogue.[3] Many developing countries, however, do not have access to some of the advanced and costly therapies, including some areas of our country. Previous studies have reported the benefit of magnesium sulphate ($MgSO_4$) as a potent vasodilator and thus having the potential to reduce high pulmonary arterial pressures associated with PPHN. Nonetheless, due to its unspecific action, its usage in PPHN remains uncommon.[4] We reported a case of PPHN managed with MgSO4 at a district hospital with limited facilities in West Papua, Indonesia.

CASE PRESENTATION

A 31-year-old woman gave birth to a normal-weight, term baby boy with a risk factor of prolonged labour and meconium stained-amniotic fluid (MSAF). The baby did not cry immediately after birth and was given initial steps of neonatal resuscitation. Apgar score was five in the first minute and seven in the fifth minute. Upon evaluation, the heart rate was 120 bpm but we found respiratory distress in the baby, characterised by nasal flaring, tachypnoea, cyanosis, severe chest indrawing, grunting and peripheral oxygen saturation (SpO_2) that was only 70% at 5 minutes of life with more than 10% difference between preductal and post-ductal sites. Total Downe's score was seven. The results of other physical examinations were within the normal limits. Hyperoxia test was performed and there was an increase of SpO_2 to 80 to 85%. Unfortunately, arterial blood gas analysis and echocardiography were unavailable in our hospital and the baby's condition was not transportable for a chest X-ray. Based on those limited findings, we concluded that the baby suffered PPHN, which may have been induced by meconium aspiration syndrome (MAS) or perinatal hypoxia due to the prolonged labour.

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Supportive oxygen therapy with continuous positive airway pressure (CPAP) was given to the baby, but there was no improvement even with the highest setting of CPAP. The oxygenation was subsequently switched to non-invasive ventilation (NIV) with peak inspiratory pressure (PIP) 30 cm H_2O, positive end-expiratory pressure (PEEP) 8 cm H_2O, respiratory rate 50, fraction of inspired oxygen (FiO_2) 100%. Surfactant and inhaled nitric oxide (iNO) were inaccessible, and due to our setting's limitation, other pulmonary vasodilator such as sildenafil or inhaled prostacyclin analogue were unavailable either. As an alternative, we gave loading dose of $MgSO_4$ 200 mg/kg BW in 30 minutes, followed by maintenance dose 20 mg/kg BW/hour to the baby. Ampicillin and gentamicin were also given as the first line antibiotics. The baby's vital signs, including blood pressure, SpO_2, and scoring of respiratory distress using Downes score were closely monitored. We decided to increase the $MgSO_4$ level to 50 mg/kg BW/hour and the SpO_2 increased to 92 to 95% after 6 hours of $MgSO_4$ infusion even though the Downes score was still five.

Routine follow-up showed improvement of the respiratory distress condition. Magnesium sulphate was reduced gradually and stopped on the fifth day of hospitalisation. At first, we encountered a problem in which the baby developed desaturation every time the FiO_2 was weaned, however, on third day of treatment, the baby's condition became more stable and the FiO_2 could be weaned, followed by the PIP and PEEP. Oxygen therapy with NIV was given for 7 days and switched to CPAP for 2 days. Fortunately, there were no side effect of hypotension or deterioration of respiratory distress in the baby. The baby was then discharged with the total 11 days stay in hospital. Further follow-up was conducted at the outpatient clinic which showed a good neurodevelopmental screening status the first three months.

DISCUSSION

PPHN is commonly present shortly after birth, precipitating severe respiratory distress and hypoxemia.[2,5] It may also be induced by a variety of primary disorders such as MAS, respiratory distress syndrome (RDS), congenital diaphragmatic hernia (CDH), neonatal sepsis, pneumonia or it can be also idiopathic.[3] In this case, MAS was thought to be the risk factor for the baby to develop PPHN due to the presence of MSAF. MAS occurs in approximately 2 to 10% of infants born with MSAF and is generally found in 25 to 40% patients with PPHN.[1,6] It can cause PPHN through maldevelopment of pulmonary vasculature pathogenesis, in which disturbance occurs in lungs that are otherwise structurally normal.[1] In such cases, infants will typically have respiratory distress with marked tachypnoea and cyanosis immediately after birth.[6] Respiratory distress is indicated with increased respiratory rate, chest indrawing, abdominal (paradoxical) breathing and is frequently accompanied with grunting and nasal flaring, which we identified in our patient. Moreover, we also found low SpO_2 with more than 10% difference of the pre- and post-ductal oxygen saturation. Hyperoxia test were also positive in our patient. It was proved by increased of SpO_2 after the patient got oxygen supplementation with 100% FiO_2. Although definitive diagnosis of PPHN is made by echocardiography, we could not perform echocardiography due to our setting limitation. Echocardiography itself is an essential test in any infant with unremitting cyanosis that is unexplained by parenchymal lung disease, to exclude structural heart disease and confirm a diagnosis of PPHN.[1] Based on those limited clinical signs and symptoms, we considered the diagnosis of PPHN and provided therapy accordingly.

The course and response to therapy in patients with PPHN vary substantially. Therefore, individualised management and frequent reassessment are critical.[3] The main goal is to decrease PVR and reduce the magnitude of the right to left shunt, mainly by administering pulmonary vasodilators.[2] Unfortunately, the standard therapies used for reducing PVR were unavailable in our hospital. Neither iNO, inhaled prostacyclin analogue, or phosphodiesterase type 5 inhibitors (sildenafil) were accessible at that time. The only choice of treatments that we had was $MgSO_4$. It is infrequent to use $MgSO_4$ as the treatment for PPHN because although it is a natural calcium channel blocker that antagonises Ca ion entry into smooth muscle so that it has the effect to dilate constricted muscles in the pulmonary arteries, its action is not specific and when given intravenously, it will act on other arteries.[4,7]

In a systematic review on MgSO4 usage in PPHN cases based on clinical grounds, all the studies demonstrated a substantial improvement in oxygenation, as measured by changes in partial oxygen pressure, alveolar-arterial oxygen index, oxygen index and alterations in mechanical ventilation needs.[4] Hypotension was seen in 16% of PPHN cases treated with $MgSO_4$.[8] A temporary drop in blood pressure 2 hours after starting the infusion was observed, which normalised after 8 hours. In several studies, inotropic agents were administered to most of the patients.[4] Dopamine commenced at 5 to 10 µg/kg BW/minute was used before the loading dose of $MgSO_4$ to prevent the systemic hypotension in one of the studies.[8] Other adverse effect was also observed, including a transient bradycardia that was corrected by dobutamine infusion, urinary retention and altered gastrointestinal tract function in about 8% of patients.[4,8]

Therefore, close monitoring should be done in patients with $MgSO_4$ therapy for any life-threatening adverse events such as bradycardia, hypotension and cardiorespiratory failure.[4] We decided to give $MgSO_4$ loading dose 200 mg/kg BW three hours after birth, followed by maintenance dose started from 20 mg/kg BW/hour and titrated up the dose per one to two hours. The upper limit that we used was 50 mg/kg BW/hour because there had been an improvement in the SpO_2 level >92%. Blood pressure measurement by auscultation was done because neither invasive method or non-invasive method using automated oscillometric device were available. We did not find bradycardia or hypotension in the baby during treatment. The improvement in SpO_2 was seen in about 6 hours after continuous $MgSO_4$. That result was in accordance with previous studies that showed significant improvement of oxygenation and decrease in PVR at 72

hours after the use of $MgSO_4$.[8] We closely monitored the patient's condition using a modified protocol that involved checking the patient's vital signs, including blood pressure, every hour and assessing respiratory status using Downe's score. In an ideal setting, we should also have monitored the serum level of magnesium and adjusted the dosage accordingly to maintain the magnesium concentration between 7 and 11 md/dL.[10]

Comparison between MgSO4 with the standard treatments such as iNO, extracorporeal membrane oxygenation (ECMO), and sildenafil was still limited. Studies comparing clinical efficacy of intravenous $MgSO_4$ and oral sildenafil in PPHN showed that sildenafil was more effective in terms of the time for oxygenation improvement, duration of mechanical ventilation, and fewer requirements of inotropic support. Both groups showed a significant improvement in their pulmonary artery pressure 48 hours after therapy as compared to their baseline measurements. However, the estimated pulmonary arterial pressure was significantly lower 5 days after therapy in neonates receiving sildenafil as compared to those receiving $MgSO_4$.[7,10] iNO is widely recognised as the primary and extensively studied treatment for PPHN, acting locally as a pulmonary vasodilator in pulmonary artery smooth muscle cells. A meta-analysis of several randomised controlled trials compared the use of iNO with control in term or late preterm newborns with PPHN. The analysis revealed no significant difference in mortality; however, there was a notable decrease in the requirement for ECMO. Furthermore, oxygenation significantly improved, leading to a reduced risk of neurodevelopmental sequelae and pulmonary complications.[2]

Furthermore, surfactant as the treatment for MAS was also unavailable in our hospital. Meconium is thought to have negative impact in the production of endogenous surfactant, and it is thought that administration of exogenous surfactant reduces ventilation-perfusion mismatch as well as PVR. However, surfactant is not routinely administered to all patient with MAS, but current study showed the benefits of giving surfactant to patient with severe disease who are mechanically ventilated and require high FiO_2 (>50%) and high mean airway pressure (>10 to 12 cm H_2O).[9] Due to the unavailability of surfactant, we could only give supportive therapy in our patient such as oxygenation and empiric antibiotics with ampicillin and gentamicin. Although antibiotic therapy is still debatable for its beneficial in MAS, we thought it would be more beneficial to give empiric antibiotics to the patient because we didn't have the laboratory examination for blood culture to distinguish the condition with neonatal sepsis.

Newborns with PPHN could have significant long-term morbidity, irrespective of the treatment modality. These infants are at high risk of neurological injury, multiorgan dysfunction, long-term sequelae such as neurodevelopmental, cognitive and hearing abnormalities, and even death.[1,2,5] The majority of studies reported one-year outcome of patients with PPHN treated with $MgSO_4$. None of the studies conducted a formal neurological assessment, but all reported that all survivors were developing normally.4 We were able to follow up the patient for three months after birth that showed good neurodevelopmental status. However, further follow up for the patient's condition and development in later childhood are still needed.

Although $MgSO_4$ showed good results in this case, the results may differ for each patient, depending on the underlying cause of PPHN and its severity. The limitation of our experience was that we could not do a proper monitoring for the estimated pulmonary artery pressure and patient's oxygen index (OI) which are needed for determining the severity of PPHN and adjusting the dose of $MgSO_4$. Thus, we did not have the precise time of adequate clinical response of $MgSO_4$ therapy. Serum magnesium level also could not be measured in our case.

CONCLUSION

In conclusion, treatment with magnesium sulphate ($MgSO_4$) can be considered beneficial to be used in persistent pulmonary hypertension of the newborn (PPHN). Nevertheless, in facilities that may be more equipped, the use of inhaled nitric oxide (iNO) remains the first choice for PPHN.[4] Sildenafil is also superior to $MgSO_4$ in terms of shorter duration of mechanical ventilation, interval to improvement of arterial blood gases, lowering estimated pulmonary artery pressure, and also the need of inotropic agent.[7,10] Vital sign, including blood pressure, SpO_2, and worsening of respiratory distress should be monitored during $MgSO_4$ infusion. This case is expected to be a reference for the beneficial effect of $MgSO_4$ usage in PPHN in other limited healthcare facilities.

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DECLARATIONS

The authors have no conflict of interest to declare.
Consent for the publishing of this case report was obtained from the patient's parents

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