Neonatal Hypermagnesemia After in Utero Exposure to Magnesium Sulfate: Case Report

Hipermagnesemia Neonatal Após Exposição *in Utero* a Sulfato de Magnésio: Caso Clínico

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Abstract

Magnesium sulfate (MgSO4) is currently the treatment of choice for severe preeclampsia and eclampsia. However, the risk and potential effects of neonatal hypermagnesemia are not well- recognized. The authors report the case of a late preterm male neonate whose mother was treated with MgSO4 for severe preeclampsia. Maternal hypermagnesemia, hypertension, and neurological worsening motivated emergency cesarean section. At his first minute of life, the newborn was bradycardic, cyanotic, hypotonic, and did not start to breathe spontaneously. Neonatal resuscitation was performed, requiring endotracheal intubation and immediate admission to the Neonatal Unit for mechanical ventilation and continuous cardiorespiratory monitoring. The immeasurable plasmatic magnesium level was compatible with the diagnosis of hypermagnesemia. Symptoms and signs slowly disappeared as magnesium values normalized and respiratory function was fully recovered hours later. This case shows a rare but reversible cause of neonatal respiratory depression and hypotonia in the context of maternal MgSO4 infusion.

Resumo

O sulfato de magnésio (MgSO4) é, atualmente, o tratamento de escolha para pré-eclâmpsia grave e eclâmpsia. Contudo, os riscos e potenciais efeitos adversos decorrentes da sua utilização não são muito reconhecidos. Os autores reportam o caso de um recém-nascido prematuro tardio, cuja mãe foi diagnosticada com pré-eclâmpsia grave e medicada com MgSO4. O agravamento neurológico, a hipertensão e a hipermagnesemia maternas justificaram a realização de cesariana emergente. Ao primeiro minuto de vida, o recém-nascido apresentou-se bradicárdico, hipotónico, cianótico e sem respiração espontânea. Procedeu-se a reanimação com intubação endotraqueal e admissão imediata na Unidade de Neonatologia para ventilação mecânica e monitorização cardiorrespiratória contínua. O valor sérico de magnésio encontrava-se acima do valor máximo doseável, compatível com o diagnóstico de hipermagnesemia. Com a normalização dos valores de magnésio houve melhoria clínica progressiva e recuperação da função respiratória algumas horas depois. Este caso ilustra uma causa rara e reversível de depressão respiratória e de hipotonia neonatal a ser considerada no contexto de infusão materna de MgSO4.

Keywords: Infant, Newborn, Diseases; Magnesium/blood; Magnesium Sulfate/adverse effects; Pre-Eclampsia/drug therapy

Palavras-chave: Doenças do Recém-Nascido; Magnésio/sangue; Pré-Eclâmpsia/tratamento farmacológico; Sulfato de Magnésio/efeitos adversos

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Introduction

Magnesium (Mg^{2+}) is the fourth most abundant cation and plays an essential role in various intra and extracellular processes. It is involved intracellularly in the activation of multiple enzymatic processes and, extracellularly, magnesium ions may block neurosynaptic transmission and interfere with acetylcholine release causing smooth muscle relaxation.[1,2]

Newborn serum concentration levels above the reference range (1.8 - 2.5 mg/dL) may cause clinical manifestations that should prompt medical attention. Possible causes of neonatal hypermagnesemia are related to prescription errors during treatment of hypomagnesemia or parenteral nutrition, use of enemas or anti-acids containing magnesium salts[3] and *in utero* exposure to magnesium sulfate (MgSO4), the current treatment for severe preeclampsia and eclampsia.[3]

Neonatal hypermagnesemia is a rare and not well-recognized entity. The authors describe the clinical course of a newborn with symptomatic hypermagnesemia induced by maternal treatment with MgSO4 due to severe preeclampsia with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count).[4] A brief revision of the literature will be presented, as well as a therapeutic approach.

Case Report

The authors present the case of a late preterm male newborn (36 weeks gestation), the first child of a healthy 23-year-old Indian mother, and non-consanguineous parents. They had moved to Portugal at the beginning of the second trimester of pregnancy and obtained adequate antenatal care in General Practice. At 35 weeks and six days of pregnancy, the mother was hospitalized due to severe preeclampsia (intense headache, hypertension, high creatinine level of 1.4 mg/dL) and HELLP syndrome. She was treated with MgSO4, receiving a loading dose of 4g intravenously for 20 minutes and a maintenance dose of 2 g/hour. However, hours later, because of maternal hypertension worsening (blood pressure 187/120 mmHg), hypermagnesemia (Mg^{2+} >9.5 mg/dL), and neurological deterioration, an emergency cesarean section was performed. A child with a low birth weight (1865 g, < percentile 3) was born, and no apparent congenital abnormalities were observed. He was bradycardic, floppy, and did not start to breathe spontaneously (Apgar score 2 at first minute of life). Neonatal resuscitation was performed using intermittent positive pressure ventilation via face mask followed by endotracheal intubation. The newborn was then transferred to the neonatal unit, requiring mechanical ventilation and continuous cardiorespiratory monitoring. On admission, he continued to be lethargic and not breathing spontaneously. Laboratory work-up, including blood gases, were normal, except for immeasurable plasmatic Mg^{2+} (>9.5 mg/dL). Treatment with calcium gluconate 10% (100 mg/kg) and furosemide (2 mg/kg) was started, and plasmatic Mg^{2+} slowly decreased. During the first 6 hours of life, he gradually became more reactive, improved muscle tone, and showed spontaneous eye opening and respiratory movements. He was extubated and placed on nasal continuous positive airway pressure (nCPAP) for another seven hours. On the second day of life, the Mg^{2+} level was normalized, and the newborn was eupneic and neurologically well. Cranial ultrasound revealed pronounced periventricular hyperechogenicity and periventricular and intraventricular hemorrhage grade 1 without ventricular dilation. Throughout his hospital stay, he kept normal vital signs, no arrhythmias, proper bowel function, adequate diuresis, and electrolyte balance. He was discharged on the 14th day of life after adequate weight gain and feeding autonomy.

Discussion

Preeclampsia, a multisystem disorder presenting as new-onset hypertension and proteinuria, complicates 5% to 7% of pregnancies.[5] Although the outcome is often good, preeclampsia is a major cause of morbidity and mortality for women and their children.[6]

MgSO4 is commonly used in obstetric practice for maternal and fetal neuroprotection, currently being the treatment of choice for severe preeclampsia and eclampsia.[6-8] The neonatal effect of in utero exposure to MgSO4 is controversial, but previous studies suggested that intrauterine MgSO4 may increase the risk of early complications, such as neonatal hypermagnesemia, hypotonia, respiratory failure, feeding intolerance, intraventricular hemorrhage, cardiac failure, and patent ductus arteriosus.[9,10] MgSO4 crosses the placenta, and, as a result, the cord blood concentration approximates the maternal serum concentration.[11,12]

The effects of MgSO4 on neonates were first studied more than 40 years ago[2] and supported years later by Riaz *et al*,[13] who noted that antenatal MgSO4 exposure was related to a higher incidence of neonatal hypotonia and lower Apgar scores. More recently, neonatal hypotonia, lower Apgar scores, more frequent intubation, and increased admission to neonatal intensive care units among MgSO4-exposed neonates were seen in a cohort study by Abbassi-Ghanavati *et al*.[14] Another study including term neonates born to mothers with preeclampsia, which compared those whose mothers received MgSO4 for eclampsia prophylaxis before delivery *versus* those whose mothers did not, suggested that antenatal MgSO4 exposure was associated with an increase in neonatal intensive care unit admissions (22% x 12%, respectively).[2] The same study states that the neonates of MgSO4-exposed mothers were more likely to have

1- and 5-minute Apgar scores lower than 7, compared with neonates of non-exposed preeclamptic mothers, although it was unclear whether those lower Apgar scores were reflective of the conditions of labour, underlying comorbid conditions or an effect of MgSO4.[2] Most frequently the admission time for MgSO4-exposed infants was immediately after the delivery, reinforcing the necessity of routinely calling a pediatric team to deliveries of mothers exposed to MgSO4, or of all mothers with preeclampsia, with close attention to respiratory and neurological status.[2]

There seems to be no agreement regarding the optimal time to initiate MgSO4, the dose (both loading and maintenance), the route of administration (intravenous or intramuscular), as well as duration of therapy. However, in a published review article, it is recommended that MgSO4 should be used intravenously as a 6 g loading dose over 20 to 30 minutes, followed by a maintenance dose of 2 g/hour. The infusion should be started at the beginning of labour and continued for at least 24 hours postpartum. For women requiring cesarean delivery, the infusion should begin at least 1 hour before and continue during surgery.[15] In our case, the doses, route of administration, and frequency of MgSO4 used were in line with that recommendation.

It is essential to highlight that the Mg^{2+} is almost exclusively excreted by the kidney; therefore, the glomerular filtration rate significantly affects its excretion.[16] MgSO4 rapidly crosses the placenta, reaching high fetal plasma and amniotic fluid levels proportional to those found in maternal blood. In prolonged therapies (greater than 72 hours), fetal magnesium can even overcome the maternal level, given the immaturity of the fetal excretory system.[17] Ramsey *et al* state that women with underlying renal disease or an abnormal creatinine clearance require adjustments in the dosing regimen used and close surveillance for signs of toxicity during the Mg^{2+} infusion.[16] In our case, maternal plasmatic creatinine level was 1.4 mg/dL at admission (the standard reference value for pregnant women in the third trimester is 0.4 to 0.9 mg/dL),[18] which may have been a significant triggering factor for the development of hypermagnesemia.

The therapeutic MgSO4 range in preeclampsia is 4 to 8 mEq/L, but much higher plasmatic levels can occur. Clinical manifestations of toxicity in the mother are usually dose-dependent and vary in severity. For instance, they might include nausea/vomiting, diaphoresis, paralytic ileus, heart palpitations, headache, muscle weakness, difficulty breathing, hypothermia, hypotension, precordial pain, and even pulmonary edema. Hypermagnesemia can also lead to electrocardiographic changes (widening of QRS complex, prolonged QT intervals) or more severe ones such as sinoatrial block, respiratory paralysis (at 15 mEq/L), and cardiac arrest (at higher concentration of 25 mEq/L)[19]

In the newborn, the clinical manifestations of hypermagnesemia have a wide variability and do not strictly correlate with the level of MgSO4, as occurs in the mother. It has been suggested that this discrepancy is due to the fact that in the fetus, the volume of distribution becomes more important than the plasma level itself, making intracellular Mg^{2+} content a determinant variable.[17] As illustrated by the reported case, the main clinical signs include hypotonia and respiratory depression. Hypotonia can be seen at variable levels, ranging from a decreased suction reflex, dimmed reflexes, and weak crying to the need for respiratory support, as is exemplified in our case. From a cardiovascular perspective, a decrease in blood pressure and heart rate could also be found without reducing the cardiac output due to the compensatory increase in ventricular function.[17]

It has been observed that MgSO4 does not cause damage to white matter or increase the incidence of intraventricular hemorrhage. In fact, a decrease in the frequency of white matter lesion and cerebral palsy in newborns of low birth weight has been shown, and this is why MgSO4 is used for neuroprotection in preterm deliveries.[17] Other possible effects have been analysed, such as retinopathy of prematurity and seizures, and no relationship was found between them and the use of MgSO4. Although hypermagnesemia is associated with intestinal paralysis in adults, this was not clearly established in newborns.[17]

Management of hypermagnesemia in the newborn depends on the severity of clinical manifestations. In most cases, the symptoms and signs improve in 48 to 72 hours with supportive therapy, including ventilation maintenance, and fluid/electrolyte balance in a neonatal care unit. Some newborns may require assisted ventilation or cardiac resuscitation, so continuous cardiorespiratory monitoring is required. The feeding of these newborns should be gradual, evaluating tolerance and gastric residual volume.[17] Calcium gluconate 10% can be used to antagonize the effect of the Mg^{2+} on the nervous system. The dose ranges from 200 to 500 mg intravenously in each administration (100 mg/kg), with continuous electrocardiographic monitoring. In order to promote a more sustained decrease in serum Mg^{2+}, patients with normal diuresis and renal function may also be treated with intravenous saline infusions and furosemide. In severe cases that continue to be unstable, it is recommended exchange transfusion or dialysis. Although these are all widely used practices, there are few methodologically adequate studies that support them.[17]

Conclusion

Hypermagnesemia is a not well-recognized possible cause of neonatal respiratory depression and hypotonia that may be induced by antenatal exposure to MgSO4. Its effects in the newborn infants are usually reversible if promptly recognized, usually leaving no sequelae. Therefore, early management are of utmost importance, and the medical team should consider this diagnosis in a neonate born from a mother treated with MgSO4. Also, the presence of the pediatric team in deliveries of mothers exposed to MgSO4, or all mothers with preeclampsia, is absolutely necessary, with close attention to respiratory and neurological status of the newborn.

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