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Original Article

Magnesium as a Prognostic Factor in Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: Magnesium (Mg) is a vital element which plays a significant role in the human body. Respiratory distress syndrome (RDS) is one of the most common problems in preterm neonates. The current study aimed to investigate the role of serum Mg level as a prognostic factor in neonates diagnosed with RDS.

Methods: This case-control study was performed in Vali-e-Asr Hospital, Tehran, Iran, for two years. A total of 100 preterm infants (50 cases, 50 controls) admitted to NICU were enrolled in this study. Demographic data, serum magnesium level, therapeutic interventions, and neonatal outcomes were investigated and the obtained data were analyzed using SPSS software. P-value less than 0.05 was considered significant.

Results: Of 100 neonates, 52% were male. The mean gestational age and birth weights were 33.4 ± 2.4 weeks and 2062 ± 72 gr, respectively. The findings revealed that the mean serum magnesium level in neonates with RDS was 2.02 ± 0.57 mg/dl, while it was 2.35 ± 0.67 mg/dl for neonates in the control group (P-value=0.001). Additionally, the calculated odds ratio of 2.38 indicated a correlation between reduced serum Mg levels and the occurrence of RDS.

Conclusion: The serum level of Mg among neonates with RDS was significantly lower, but the lower level of Mg was not associated with adverse outcomes in neonates.

Keywords: Magnesium, Neonatology, Respiratory distress syndrome, Preterm neonates

Introduction

Magnesium (Mg), as an essential element in the body, plays a vital role in many physiologic and homeostatic functions. It serves as a cofactor in more than 325 enzymatic reactions, thereby exerting influence over essential functions. Among these are control of vasomotor tone, modulation of neuronal activity, and facilitation of muscle contraction, all of which compose a fundamental dimension of its role in human biology (1). Moreover, Mg is crucial in the immune system and interferon signaling pathway (2). Although less than 1% of total Mg is found in the blood, serum Mg could demonstrate Mg status (3). Mg exists in blood in many forms; however, the ionized form (Mg^{2+}) is the most biologically crucial (1).

Many studies evaluated serum Mg levels in neonatal diseases, including neonatal hyperbilirubinemia, neonatal acidosis, perinatal asphyxia, and hypoxic-ischemic encephalopathy. Notably, instances of hypoxia, acidosis, and cellular injury may cause hypermagnesemia due to the Mg exchange between the intra and extracellular spaces. Empirical evidence has revealed lower levels of Mg in neonates who suffer from birth asphyxia, compared to normal neonates (4,5). Furthermore, infants with hypoxic-

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ischemic encephalopathy had remarkably lower serum Mg levels (6).

Both hypomagnesemia and hypermagnesemia are associated with acute respiratory failure in adults. Hypomagnesemia can potentially contribute to respiratory failure by decreasing the acetylcholine secretion in terminal neurons, and hypermagnesemia may reduce the depolarizing action of acetylcholine at the neuromuscular junction (7). Respiratory distress syndrome (RDS) in neonates is a common problem, especially in preterm infants. This syndrome is caused by a lack of surfactant synthesis or its inactivation, coupled with structural immaturity of the lungs. Notably, RDS is the leading cause of respiratory failure and death in newborn infants (8).

Some studies have indicated the association between increased levels of Mg and RDS (9), pulmonary interstitial emphysema in the extremely low birth weight, respiratory failure, and later development of Bronchopulmonary Dysplasia (BPD) (10). Low Mg level is associated with impaired respiratory functions, with reports indicating that patients afflicted with acute pulmonary ailments experience hypomagnesemia (7,10).

Pregnant women are at risk of Mg deficiency due to its low intake. Hypomagnesemia has been found among preterm neonates and those affected by RDS (10). Nevertheless, the available data pertaining to alterations in serum Mg levels in neonates with RDS remains unclear.

Given the importance of RDS and limited studies in this area in Iran, the current study aimed to investigate the role of serum Mg level as a prognostic factor for neonates affected by RDS.

Methods

The current research was a retrospective unmatched case-control study carried out in Vali-e-Asr Hospital, Tehran, Iran, from October 2017 to September 2019.

This study included preterm infants with a gestational age of fewer than 37 weeks, all of whom were diagnosed with RDS based on clinical symptoms. These symptoms included tachypnea, nasal flaring, expiratory grunting, sub and intercostal retractions, reduced or absent breath sounds, cyanosis, and increased oxygen requirement. The diagnosis was further supported by chest X-ray results (a diffuse ground glass reticulogranular appearance with air bronchogram and low lung volume). Infants meeting these criteria and requiring mechanical ventilation and surfactant administration were included in the study. For comparative purposes, preterm newborns with a gestational age of fewer than 37 weeks without RDS who were born in the same period were randomly selected and enrolled as the control group. All neonates were hospitalized in NICU, and informed consent was obtained from the parents of each neonate. Preterm infants born to mothers with underlying medical conditions (such as preeclampsia, diabetes, prolonged rupture of membranes, chorioamnionitis, or gastrointestinal problems) were excluded from the study. Additionally, infants exposed to magnesium sulfate as a tocolytic agent, those with intrauterine growth restriction, congenital malformations, chromosomal anomalies, intrauterine infections, or those who died shortly after birth were excluded from the study.

Sample Size

The sample size was estimated by considering the 95% confidence level and 80% power of the study. This estimation was based on a study conducted by Sarici et al (9). In their study, a mean Mg level was found to be 0.8±0.4 in RDS and 0.57± 0.13 mmol/l in control groups. The required sample size was estimated to be 30 patients in each group.

$$N = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \left(SD_1{}^2 + SD_2{}^2\right)}{(\mu_1 - \mu_2)^2}$$

$$Z_{1-\alpha/2} = 1.96$$

$$Z_{1-\beta} = 0.84$$

$$SD_1{}^2 = 0.4$$

$$SD_2{}^2 = 0.13$$

$$\mu_1 = 0.8$$

$$\mu_2 = 0.57$$

A total of 100 eligible neonates were enrolled in this study, of whom 50 neonates were the case, and 50 neonates were the control group. Upon admission, a serum sample was collected from each neonate to measure Mg levels. This sample was obtained concurrently with other standard blood tests, including complete blood count and biochemistry parameters. The serum Mg level was measured using the spectrophotometric device. Demographic information, including gestational age, sex, birth weight, mode of delivery, serum magnesium level, illness severity, therapeutic interventions (surfactant therapy, respiratory support, inotrope infusion), and outcomes were collected.

Data analysis

The collected data were analyzed using the

SPSS version 23 database with a confidence interval of 95%. P value less than 0.05 was considered statistically significant. The power of the study was 80%.

Analytical statistics include a quantitative comparison of data between the groups. Before comparing the quantitative variables between the categories, the normal distribution of data was examined using Kolmogorov-Smirnov test. Since the data were not distributed nroemally, the Mann-Whitney test wass employed to compare the groups. Comparison of qualitative variables between groups was performed using the Chi-square test, and correlation between quantitative variables was assessed with the Spearman test.

Multivariable logistic regression was used for the adjustment of confounding factors. In this way, the variables that showed a significant difference in the analysis and pair-by-pair comparisons, as well as those that were obtained in the analysis with a p-value of <0.2, were included in the model. In the binary regression model, quantitative and qualitative variables were included as independent variables. The RDS was considered a dependent variable. Due to the small sample size, statistical tricks bootstrapping was used to provide the results reliable.

Ethical approval

This study was approved by the Ethics Committee of Tehran University of Medical Sciences according to Helsinki Declaration (approval code: IR.TUMS.CHMC.REC.1398.035). All the participants' parents provided written consent for their involvement in this study.

Results

Among 100 neonates, 52 (52%) were male, and more than 90% of the infants were delivered by cesarean section. The mean gestational age and birth weight were 33.4 ± 2.4 (26-37) weeks and 2062 ± 72 (700-3760) grams, respectively. The mean serum Mg level was 2.19 ± 0.64 mg/dl. The studied groups had no significant abnormalities in biochemistry parameters and electrolytes.

The main characteristics of the groups are shown in Table 1. Sex, birth weight, and delivery mode were similar between the two groups. There was a significant difference in terms of gestational age (p value < 0.001), the first and fifth Apgar scores (p value < 0.0001), and need for resuscitation at birth (p value < 0.001) between the case and control groups.

Table 1. The characteristics information of the two groups

Variables	Case N=50(%)	Control N=50(%)	Total N=100	P-value
Sex				
Male	27(52%)	25(50%)	52(52%)	0.689
Female	23(46%)	25(50%)	48(48%)	
Gestational age (weeks)	32.46±2.61	34.34±1.82	33.40±2.43	0.001
Birth Weight (grams)	1939±813.522	2185.70±610.642	2062.35±726.288	0.66
Delivery mode				
.NVD	2(4%)	6(12%)	8(8%)	0.269
.C/S	48(96%)	44(88%)	92(92%)	
Apgar				
.1st min	6.26±2.39	7.72±1.49	6.99±2.12	<0.0001
.5th min	8.28±1.23	9.04±0.49	8.66±1.00	
CPR requirement in delivery room	40(80%)	24(48%)	64(64%)	<0.001
Antenatal corticosteroids	44(88%)	5(10%)	49(49%)	<0.0001
Inotropes				
.1	8(16%)	4(8%)	12(12%)	0.001
.2	9(18%)	5(10%)	14(14%)	
.>2	6(12%)	2(4%)	8(8%)	
Respiratory support	50(100%)	27(54%)	77(77%)	<0.0001
Invasive ventilation	27(54%)	3(6%)	30(30%)	<0.0001
Death	10(20%)	0(0%)	10(10%)	<0.001
Mean serum Mg level (mg/dl)	2.02±0.57	2.35±0.67	2.19±0.64	0.001

Table 2. Mean serum Mg level in studied groups (mg/dl)

Variables	Case N=50	Control N=50	p-value
Sex			
Male	1.89±0.58	2.26±0.75	0.032
Female	2.17±0.54	2.44±0.58	
Delivery Mode			
.NVD	1.50±0.28	2.50±0.62	0.89
.C/S	2.04±0.57	2.33±0.68	
CPR in delivery room			
.Yes	2.07±0.60	2.18±0.68	0.13
.No	1.80±0.36	2.50±0.63	
Inotropes			
.Yes	2.08±0.64	2.18±0.61	0.70
.No	1.96±0.51	2.18±0.06	
Respiratory support			
. Non-invasive	2.09±0.58	2.22±0.50	>0.05
.Invasive	1.93±0.56	2.50±0.62	

Forty-nine neonates (44 in case and 5 in control groups) received antenatal corticosteroids. All 50 neonates with RDS received surfactant therapy. Thirty-four neonates (68%) received one, and 16 (32%) received two doses. The mean age of newborns receiving surfactant was 4.59±4.309 hours of life.

Regarding inotropic drug administration, 23 neonates (46%) in the RDS group and 11 (22.4%) in the control group received inotropic drugs received such treatment. Among the 23 neonates receiving inotropic drugs, 8 were given dopamine, 9 were administered a combination of dopamine and milrinone or dobutamine, and 6 were prescribed adrenaline or noradrenaline as the third agent. Of the 11 neonates in the control group who received inotropic drugs, 4 were administered dopamine, 5 received a combination of dopamine with milrinone or dobutamine, and 2 were prescribed adrenaline or noradrenaline in addition to the therapeutic regimen. There was a significant difference in the use of antenatal steroids, inotropes, and surfactants between the two groups.

All the neonates with RDS and 54% of controls required respiratory support. The need for invasive mechanical ventilation was significantly higher in neonates with RDS than in controls (54% versus 6%, P-value < 0.001). In addition, the mean duration of ventilator therapy was more in cases than in controls (7.01 ± 4.02 vs. 1.04 ± 0.02 days, P-value < 0.001).

The length of hospital stay differ insignificantly between the studied groups (18.91 ± 18.18 vs. 16.68 ± 13.32 days, p-value = 0.07). Neonatal mortality occurred in 20% of infants with RDS.

The mean serum Mg level in neonates with RDS and the control group was 2.02 ± 0.57 and 2.35 ± 0.67 mg/dl, respectively (P value = 0.001). The mean serum Mg level in male neonates was 2.07 ± 0.68 and 2.31 ± 0.57 mg/dl in female neonates (P-value = 0.032).

As can be seen in Tabe 2, the serum Mg level was not statistically different with regard to delivery mode (p-value = 0.89), need for resuscitation (p-value = 0.13), frequency of surfactant administration (p-value = 0.60), use of inotropic agents (p-value = 0.70) and neonatal mortality (p-value = 0.54).

Although the mean Mg level was higher (2.5913 ± 0.609 mg/dl) in neonates who did not receive any respiratory support (P-value = 0.003), there was no statistical difference observed in the mean Mg levels with respect to the type of ventilation—either invasive or non-invasive—for both the cases (P-value = 0.282) and controls (P-value = 0.107) groups.

Spearman correlation test indicated no significant correlation between serum Mg level and birth weight (r = 0.165, p-value = 0.102) and gestational age (r= 0.161, p-value = 0.109). In addition, the correlation between serum Mg level and duration of hospitalization was insignificant (r = 0.188, P-value = 0.191).

In logistic regression analysis, lower level of serum Mg (OR = 2.38, 95%CI = 1.081-5.242, p-value = 0.31) and lower gestational age (OR = 1.4, 95%CI = 1.097-1.786, p-value = 0.007) were the significant risk factors for the development of RDS (Table 3) .

Table 3. Multivariable analysis of associated factors related to RDS by the logistic regression model

Variables	B	P-value	Odds Ratio*	95% confidence interval	
				lower	upper
Apgar 5 min	1.056	0.020	2.874	1.185	6.972
Gestational age	0.336	0.007	1.400	1.097	1.786
sex	-0.081	0.871	0.922	0.345	2.465
Magnesium	0.867	0.031	2.381	1.081	5.242

To eliminate the effect of confounding and intervening variables together, we used the logistic regression test to see which variables really differ independently and separately from other variables between the case and control groups.
*: Adjusted

Discussion

The existing data regarding changes in serum g) levels in neonatal RDS are ambiguous. The current study revealed a significant relationship between RDS and a lower Mg level. The lower level of Mg was independently associated with a 2.3-fold increase in the risk of RDS development.

In the present study, neonates whose mothers received $MgSO_4$ were excluded to limit any impact of Mg exposure on the neonatal outcome. However, most researchers evaluated the effect of antenatal Mg exposure on neonatal mortality and morbidities, including RDS. It should be kept in mind that maternal Mg may influence neonatal Mg levels.

A recent study compared the short outcomes and serum Mg levels in two groups of preterm infants (GA: 28-34 weeks) exposed to antenatal Mg and those who were not. The serum Mg level was higher in the exposed than in the non-exposed group (3.10±.1.35 vs. 1.74±.0.19). The incidence of RDS with a significant difference was more elevated in preterm infants with lower Mg levels who were not exposed to antenatal magnesium (p-value = 0.013). Moreover, they found a statistical difference in gestational age between the two groups (p-value = 0.011); the lower gestational age was observed in non-exposed infants (11), which was in line with the present results.

Mirzamoradi et al. conducted a randomized placebo-controlled trial to assess the effects of Mg sulfate on the delay of active labor in women with premature rupture of membrane and subsequent fetal complications. Despite not explicitly mentioning serum Mg levels in neonates from both groups, their logistic regression findings demonstrated an 80% reduced likelihood of RDS in neonates born to mothers who received antenatal magnesium, compared to the placebo group. In contrast, no other fetal outcomes were observed in relation to antenatal magnesium exposure in their study (12). Another study failed to show the beneficial impact of antenatal Mg sulfate exposure on neonatal morbidities, such as intraventricular hemorrhage, retinopathy of prematurity, and bronchopulmonary dysplasia, except for a significantly lower rate of RDS in the exposed group (13). As the Mg sulfate may delay the active phase of labor, there is a time for antenatal corticosteroids to perform their effect. Therefore, the lower rate of RDS in exposed neonates may be explained in this wat. However, some studies revealed no difference between Mg-exposed and non-exposed infants regarding RDS (14,15).

In contrast to the present study, Sarici et al. demonstrated a higher ionized Mg (IMg) level in the RDS group, compared to controls (0.8±.0.4 versus 0.57±.0.13 mmol/l). Moreover, an increased IMg level was associated with postnatal acidosis and base deficit in the neonates with RDS, compared to the control group (9). Several studies have indicated that hypoxia, acidosis, and cellular injury might cause an exchange between intracellular and extracellular Mg and result in hypermagnesemia (4,9,16). However, there is an association between hypomagnesemia and severe asphyxia (6). As RDS may be characterized by some degree of hypoxia and acidosis, it seems that both high and low levels of serum Mg may be seen in RDS. Furthermore, it should be considered that renal clearance of Mg is decreased in preterm infants, potentially resulting inand may lead to a higher level of Mg (13). Further studies should be designed to evaluate changes in serum Mg levels in neonatal RDS.

The major risk factors for RDS are low gestational age and birth weight. RDS has a slightly male predominance (17). In the present study, RDS was more common in males, and they had a lower level of Mg than their female counterparts. Hypomagnesemia was observed in critically ill children admitted to PICU and was significantly associated with the male gender (p = 0.001). They considered it as male predominance in their society field (18). Sarici et al. did not mention gender predominance in RDS or plasma IMg level field (9). More studies should be done focusing on Mg level regarding gender.

Antenatal corticosteroid and surfactant therapy dramatically changed the management of RDS and improved the outcome. The European consensus guidelines recommend a single course of antenatal corticosteroid in anticipated preterm delivery until 34 weeks of gestation and early surfactant administration as soon as possible when it is necessary to field (19).

In the present study, about 90% of the patients with RDS received antenatal corticosteroids, and all had surfactant administration. One-third of neonates with RDS received more than one dose. Supportive care was implemented for all the subjects. Intervention with inotropic agents was more common in cases. This study did not reveal any correlation between lower Mg levels and different therapeutic options.

European consensus guidelines recommend non-invasive ventilation in treating RDS; if it fails, mechanical ventilation should be considered (19).

In the present study, all 50 neonates with RDS required respiratory support, 46% received non-invasive, and 54% received invasive ventilation. Although the mean duration of ventilatory therapy was longer in this group, the hospital stay time was not different between the two groups. The higher Mg level was observed in neonates who did not need any respiratory support. The current results demonstrated a lower level of Mg in the RDS group who received non-invasive than those who received invasive ventilation, however, the difference was not statistically significant. Aditiawarman et al. compared the respiratory outcome in the studied preterm infants regardless of exposure to MgSO4 at three different levels of Mg (<2.5 mg/dl, <2.5 - >3.5 mg/dl, and >3.5 mg/dl). Most patients either on CPAP or mechanical ventilation were in the lower Mg level group (<2.5 mg/dl), and no significant difference was observed between the two non-invasive and invasive ventilation field modes (11). These results were similar to those obtained in the current study.

The present research revealed no significant correlation between Mg level on admission and PICU outcomes regarding the duration of hospital stay, need, and duration for mechanical ventilation, discharge, and death field (18). Another research evaluated the admission serum Mg level of adult patients with acute respiratory failure who required mechanical ventilation. They reported hypomagnesemia (<1.5 mg/dl) and hypermagnesemia (>2.3mg/dl) at the time of admission. They had an increased risk of acute respiratory failure requiring mechanical ventilation with an odds ratio of 1.6 and 1.4, respectively. However, the patient population was heterogeneous in these two recent studies. The pathophysiology and etiology of diseases differed from neonatal infants, and the results could not be generalized. More homogenous studies are warranted on this issue.

In the current study, all the mortality occurred in the RDS group, which was significantly higher than in controls. There was no correlation between mortality and Mg level. Saric et al. expressed higher IMg levels in neonates with expired RDS. However, they suggest that this outcome was more related to complications of prematurity and the nature of the disease rather than Mg level (9).

Although the present study was one of the scarce studies that evaluated serum Mg levels in preterm infants with RDS, it is important to acknowledge several limitations. The sample size was small and the study itself was retrospective and single-center research. Notably, the absence of measurements for ionized magnesium, which represents the most biologically and physiologically active form of magnesium, stems from the requirement for specialized equipment that is often unavailable in typical clinical environments. The scarcity of relevant literature on this specific topic contributes to the heterogeneity observed in the studies that were included.

Conclusion

In conclusion, this study demonstrated lower serum Mg levels in neonates with RDS, compared to the control group. There was no correlation between serum Mg level and neonatal outcomes. The findings underscore the necessity for more comprehensive investigations, ideally with larger sample sizes. Such studies can deepen the understanding the role of serum Mg level in neonatal RDS and its outcome/ This, in turn, could potentially lead to more precisely targeted interventions aimed at mitigating the array of morbidities experienced by preterm infants.

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Conflicts of interest

The authors declare no conflict of interest.

Founding

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