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Maternal Magnesium Level Effect on Preterm Labor Treatment

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Abstract

Objectives: This study intended to compare the serum magnesium level in women with preterm labor, with its level in women with normal pregnancy of the same age, and assess the relationship between serum magnesium level and response to magnesium sulfate (MgSO4).

Materials and Methods: Forty women aged 18-40, with gestational age of 26-32 weeks and signs of preterm labor, and 40 women in similar age and gestational age with normal pregnancy were included in this study. Case group received betamethasone 12 mg in 2 separate doses with 24-hour interval. MgSO4 was administrated (in dose of 4 mg), and continued by 2 mg/h. Once the tocolytic therapy goal was achieved, the administration of MgSO4 continued for an additional 12-hour.

Results: The mean age, gestational age, gravidity, parity, number of live born children, number of dead children, miscarriage, and molar pregnancy were similar in 2 groups. The mean of serum magnesium level showed a significant difference between 2 groups. In the case group, 27 patients showed positive therapeutic response to MgSO4; the difference between the mean of serum magnesium level in these 27 patients and the other 13 patients who did not respond well was significant. The serum magnesium level < 1.85 mg/dL as a cut-off point had 85% sensitivity and 78% specificity with CI = 0.75-0.97 in predicting response to MgSO4 in the case group.

Conclusion: Serum magnesium level can be used as a predictive tool for preterm labor. It can help in preterm labor in selecting patients who benefit from MgSO4 as a tocolytic agent. Magnesium supplementation may be helpful in patients with decreased serum magnesium level to prevent preterm labor.

Keywords: Maternal magnesium, Preterm labor, Magnesium sulfate

Introduction

Preterm birth is the leading cause of neonatal mortality and morbidity in the world (1,2). In the United States almost 1 out of 8 babies is born before 37th weeks of gestational age(3). Besides increased neonatal mortality and morbidity, preterm birth causes long-term sequels for both the mother and the baby (4). The World Health Organization (WHO) defines the preterm labor as the labor which starts before the 37th completed week (<259 days) of gestation, counting from the first day of the last menstrual period (5, 6). Preterm labor is recognized by frequent uterine contractions leading to progressive cervical changes, which occurs in 10%–15% of all pregnancies (7).

The exact cause of preterm labor is not known and multifactorial etiology is suggested (8). Although many risk factors are identified, it occurs spontaneously without any special risk factor in 50% of cases (8). The main cause of preterm labor is preterm rupture of membrane. Other suggested risk factors include infection, multiple gestations, hypertension, anemia, cervical incompetence, prepartum hemorrhage, anomalies of fetus or uterine, heavy work, and smoking (9,10). Some studies have also suggested socio-economic and geographical location as risk factors (9,10).

In line with different suggested etiologies a change in cellular basic biochemical function caused by a change in micro and macro minerals is also proposed (11). Although these trace elements do not play any direct role in the etiology of preterm labor, they may have an indirect role in the etiopathogenesis of preterm labor (12). Among the trace elements, magnesium has received the highest attention (13). Decreased serum magnesium level could probably decrease the magnesium level in myometrium which could lead to uterine hyperactivity followed by cervical dilatation (14,15).

In the women with preterm labor, the most beneficial intervention is antenatal corticosteroids. Corticosteroids have been proved to reduce neonatal mortality and morbidity (16). The main goal of tocolytic therapy is to maintain the pregnancy for at least 48 hours, which provides time for administration of antenatal corticosteroids. Magnesium sulfate (MgSO4) is currently the most commonly used tocolytic agent in the United States (17). Some recent studies have recommended prophylactic oral magnesium supplementation as an inexpensive way of decreasing risk of preterm labor among all pregnant women or those at higher risk (10,14).

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In this study, we aimed to evaluate serum magnesium level in women with gestational age of 26-32 weeks and signs of preterm labor, and compare it with serum magnesium level in women with normal pregnancy of the same age. We also aimed to assess the effect of MgSO4 as a tocolytic agent in delaying labor for at least 48 hours and to evaluate the relationship between serum magnesium level and response to MgSO4.

Materials and Methods

This study was conducted in 3 hospitals (Ghaem, Emam Reza, and Omolbanin) affiliated with Mashhad University of Medical Sciences (MUMS) from March 2014 to December 2015. Forty women, aged 18-40 years, with gestational age of 26-32 weeks and sings of preterm labor were included in the study. The control group consisted of 40 women in similar age and similar gestational age referred for the routine pregnancy control. In the event of preterm labor in 32-34 weeks of gestational age, other effective tocolytic agents with easier route of administration including nifedipine is indicated and neuro-protection of MgSO4 is required before 32 weeks of gestation, therefore, we excluded patients with pregnancy longer than 32 weeks from the study.

The inclusion criteria consisted of a history of 2 or more regular uterine contractions lasting for 45-90 seconds per 10 minutes (at least 180 Montevideo units), accompanied by a cervical change in women with gestational age of 24-32 weeks. The exclusion criteria were as follows: multiple gestations, endocrine or renal disorders, uterine anomaly, uterine leiomyoma, history of recurrent abortion, previous preterm labor, cerclage, infant with low birth weight, premature rupture of membrane, and hypertension. Patients with contraindication to tocolytic therapy such as fetal death, fetal anomaly, myasthenia gravis, chorioamnionitis, severe preeclampsia, and severe bleeding were also excluded from the study. Women who had used calcium and magnesium supplementations during pregnancy were also considered disqualified. The participants' information was collected by a checklist.

Three milliliters blood sample was taken from all participants. Serum magnesium level was assessed by BT 3500 Chemistry analyzer with colorimetric method. Uterine contraction and fetal heart beat was monitored by Bionet Twin View FC1400 Fetal Monitor, which had a probe for monitoring fetal heart rate and another tocodynamometer for evaluating uterine contraction. Cervical dilatation was evaluated by physician before the start of the treatment.

The women in the study group (with preterm labor) received Betamethasone 12 mg in 2 separate doses with 24-hour interval. Serum magnesium level was evaluated before starting MgSO4 administration. One bolus dose of 4 mg MgSO4 was administrated to the patients and the administration was continued by 2 mg/h. The infusion rate was modified based on the patients' clinical response. In resistant cases, the infusion dose increased up to 3 mg/h. Patients were constantly monitored for blood pressure, pulse rate, breathing rate, uterine contraction, patellar reflex, urine output, and serum magnesium level. Once the tocolytic therapy goal was achieved and uterine contractions were stopped, the administration of MgSO4 continued for an additional 12-hour. Tocolytic therapy was considered successful in case of delaying pregnancy for at least 48 hours. Collected data were inserted into SPSS version 15.0 and analyzed by appropriate statistical tests. The significance level was considered less than 0.05 in all calculations.

Results

In the present case-control study, 40 pregnant women with preterm labor in gestational age of 26-32 weeks, and 40 women with normal pregnancy in the same gestational age were included. The mean age of case group was 29.36 ± 4.69 years and the mean age of control group was 30.37 ± 4.47 years which had no statistical significant difference ($P=0.67$). There were also no significant differences between the case and control groups with respect to the gestational age ($P=0.38$), gravidity ($P=0.38$), parity ($P=0.44$), number of live born children ($P=0.52$), number of dead children ($P=0.78$), miscarriage ($P=0.72$), and molar pregnancy ($P=0.84$) (Table 1).The mean and standard deviation of serum magnesium level in the case group was 1.80 ± 0.17 and in the control group was 1.97 ± 0.19, which demonstrated a significant difference ($P=0.04$; Table 1).

Out of 40 women with preterm labor, 27 showed positive therapeutic response to MgSO4; the uterine contraction was stopped and the delivery was delayed for at least 48 hours. The difference between the mean of serum magnesium level between 27 patients who responded to MgSO4 and the other 13 women who did not respond, was significant ($P<0.005$; Table 2).

The predictive value of serum magnesium level for predicting response to MgSO4 as a tocolytic agent was calculated by ROC curve. It was shown that serum magnesium level <1.85 mg/dL as a cut-off point had 85% sensitivity and 78% specificity with CI = 0.75-0.97 in predicting response to MgSO4 (Figure 1).

Table 1. Comprision of Different Varibles Between 2 Groups

Variable	Case	Control	*P*
Age (y)	29.36 ± 4.69	30.37 ± 4.47	0.67
Gestational age (wk)	30.27 ± 2.63	29.00 ± 1.41	0.38
Gravidity, Min-Max	1-6	1-5	0.38
Parity, Min-Max	0-6	0-5	0.44
Live born children, Min-Max	0-3	0-2	0.52
Dead children, Min-Max	0-3	0-2	0.78
Miscarriage, Min-Max	0-3	0-2	0.72

P value < 0.05: significant.

Table 2. The Mean and Standard Deviation of Serum Magnesium Level Between Case and Control patients, and Respondent and Non-respondent Women

Group	Number	Mean ± SD	*P* value
Control group	40	1.97 ± 0.19	0.04
Case group	40	1.80 ± 0.17	
Cases responded to MgSO4	27	1.75 ± 0.16	< 0.005
Cases not responded to MgSO4	13	1.95 ± 0.15	

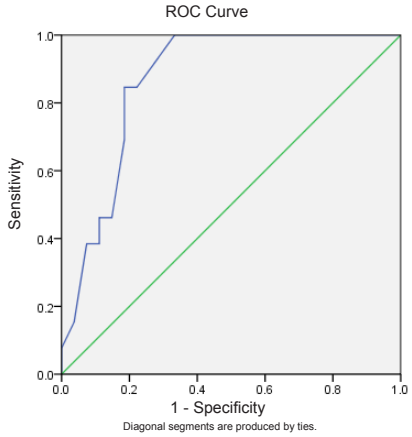

Figure 1. ROC Curve for Maternal Serum Magnesium Level <1.85 mg/dL in Preterm Labor for Predicting Response to MgSO4.

Discussion

Preterm labor is the leading cause of neonatal mortality and morbidity and is responsible for one third of infant deaths (18,19). Unfortunately the incidence of preterm labor has been increased by 30% since 1981 (17). The health care costs of prematurity are high (2,20) and it causes serious long-term problems for both mother and infant (4).

The first line of intervention used in preterm labor is antenatal corticosteroids, which has been shown to reduce neonatal mortality and multiple morbidities (21,22). Scarce data exists proving that tocolytic therapy directly concludes in neonatal outcomes (23). However, researches show that short-term tocolytic therapy is more effective than placebo in prolonging pregnancy for at least 48 hours (21,24). Thus, tocolytic therapy is used with the purpose of maintaining the pregnancy for at least 48 hours with the intention of enabling administration of antenatal corticosteroids, and maternal transport to a more equipped center if required (12).

Many different classes of drugs have been introduced and examined as tocolytic agents including betamimetics, MgSO4, prostaglandin inhibitors, calcium channel blockers, oxytocin receptor antagonists, and so on (12). However, there is no clear "first-line" tocolytic drug for managing preterm labor (12,25,26). In the hospitals of MUMS, MgSO4, adulate, and indomethacin are used as tocolytic drugs.

Since magnesium has an inhibitory role in myometrial contractions, attention has been paid to the role of magnesium deficiency in causing preterm labor. MgSO4 was first used as a tocolytic agent by Steer and Petrie in 1977, on 77 women with preterm labor. The success rate was 77% compared with 45% and 44% in using ethanol and placebo, respectively (27). The exact mechanism of magnesium action is not understood. Probably the inhibitory effect of magnesium on preterm uterine contractions is related to the antagonism of calcium-mediated uterine contractions (28).

The aim of this study was to compare the serum magnesium level of women in preterm labor with women who had normal pregnancy in similar gestational age, and to find any possible association between serum magnesium level and response to MgSO4 as a tocolytic agent.

Forty women with gestational age of 26-32 weeks and signs of preterm labor, and 40 pregnant women in the same gestational age were included in the study. The data analysis showed no statistically significant difference between the case and control groups in their chronological age, gestational age, number of pregnancy, number of deliveries, number of live born children, number of dead children, history of miscarriage, and history of molar and ectopic pregnancy.

In their studies, Shahid et al (29) and Okunade et al (8) did not find any significant difference between cases and controls in the age, parity, and history of miscarriage. Kamal et al declared that age and parity had no significant relationship with serum magnesium level (13) and they were similar in 2 groups. Accordingly, Gupta et al reported that serum magnesium level in the case and control groups were independent of the factors like maternal age, parity, and gestational age (14). The results of the current study also showed that despite the significant difference in the serum magnesium level of 2 groups, the participants' age, gravidity, parity and gestational age were similar.

Neither of the above-mentioned studies found a significant relationship between the age and preterm labor; this result is similar to our study. Cunningham et al reported a significant association between the age and preterm labor in their study (30). The difference between the results of the present study and Cunningham's may lie in patient selection factor. The patients in Shahid et al, Okunade et al and the current study were all selected from the women who had referred to public state centers, while in Cunningham's study women were selected from patients who had attended the private hospitals and, correspondingly, belonged to an almost high socio-economic class of society.

In their study, Bhat and Waheed evaluated the relationship between socio-economic class and preterm labor and found a significant association between low socio-economic class and preterm labor ($P < 0.05$) (31). They also found a significant difference in serum

magnesium level between 3 groups of high, medium, and low socio-economic classes. All the participants were selected from patients referred to public hospitals; hence, they were expected to belong to low socio-economic class. Therefore, no evaluation of this area could be made in this study.

The statistical analysis in the present study showed a significant difference between the case and control groups in terms of serum magnesium level (1.97 ± 2.40 mg/dL vs. 1.80 ± 0.17 mg/dL, $P = 0.04$). Similar findings were reported by Shahid et al (29), Uludag et al (25), Okunade et al (8), Kamal et al (13), Bhat and Waheed (31). In Okunade's study, the mean of serum magnesium level was 1.73±0.4 versus 1.93 ± 0.4 mg/dL in the case and control groups, respectively (8). Shahid et al also found a significantly lower serum magnesium level in women with preterm labor compared to that in the women of control group (1.60 ± 0.466 vs. 1.87 ± 0.3) (29). In the studies of Kamal et al and Begum et al, serum magnesium level in women with preterm labor was reported significantly low as 1.4 ± 0.22 SD and 1.77 ± 0.36, respectively (13,32). Kamal et al suggested that serum magnesium level could be used as a valuable predictive tool for preterm labor. Bhat et al reported a significant reduction in the serum magnesium level in women with preterm labor compared to control group women as 1.34 ± 0.09 versus 1.875 ± 0.013. Gupta et al also found similar results (1.47 ± 0.49 vs. 2.81 ± 0.52) (14).

In the current study, given the response to MgSO4 as the tocolytic agent, 27 out of 40 women with preterm labor had a positive response, which means that their contraction was significantly decreased for at least 48 hours. The comparison of serum magnesium level between these women and the remaining 13 women who did not respond to treatment indicated a significant difference (1.75 ± 0.16 vs. 1.95 ± 0.15, $P<0.05$).

In the study of Uludag et al, the magnesium level <1.75 mg/dL was considered as a cut-off point for predicting the response to MgSO4 as a tocolytic drug. They reported sensitivity and specificity of 80% and 84.1%, respectively, with 83% accuracy (25). In the study of Okunade et al, serum magnesium level <1.6 mg/dL was considered as a cut-off point for predicting preterm labor, which had sensitivity and specificity of 50% and 52%, respectively (8). In the present study, the predictive value of serum magnesium level in women with preterm labor for predicting the response to MgSO4 was evaluated by Roc curve. It showed that serum magnesium level <1.85 mg/dL as a cut-off point had 85% sensitivity and 78% specificity with CI = 0.75-0.97 in predicting the response to MgSO4.

The results of our study indicated that serum magnesium level in women with preterm labor could predict patient response to MgSO4 as a tocolytic agent. In their study, Uludag et al reported similar findings and concluded that basal serum magnesium level had a predictive value in evaluating MgSO4 response to tocolysis (25). Other studies suggested that serum magnesium level in pregnancy could be a valuable tool in predicting preterm onset of labor (29,30) and some suggested prophylactic oral magnesium supplementation in women with higher risk for the development of preterm labor (8,14,32).

Limitations

The probable maternal and neonatal side effects caused by MgSO4 were not evaluated. Moreover, the overall neonatal outcome was not evaluated either.

Conclusion

Based on the findings of the current study, serum magnesium level can be used as a predictive tool for preterm labor. It seems serum magnesium evaluation must be carried out in pregnant women in order that high risk preterm labor be predicted and prevented. Measurement of magnesium may also help in the cases of preterm labor to select patients who benefit from MgSO4 as a tocolytic agent.

Future studies are warranted in order to investigate the effect of magnesium supplementation in the patients with decreased serum magnesium level to prevent preterm labor.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

Ethical Issues

The study protocol was approved by the Ethic Committee of MUMS (ethical code: 930267). Written consent was obtained from participants.

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