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UMBILICAL CORD SERUM MAGNESIUM LEVEL AND NEONATAL OUTCOME IN GROUP OF NEONATES AT 30-34 GESTATIONAL AGE*

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Abstract

Background

Magnesium, as a well-known calcium antagonist, is widely used in perinatology (as a magnesium sulphate) for imminent eclampsia as well as tocolytic agent. Some authors indicate that antenatal magnesium treatment could result in neuroprotection in VLBW neonates (1500 g). It was also revealed that maternal magnesium treatment produces beneficial effect on a newborn's condition after birth, assessed according to SNAP.

Aim of study

To find correlation between the umbilical serum cord magnesium concentration in a group of newborns without antenatal exposition to magnesium sulphate and the neonatal outcome as well as to compare the neonatal outcome of babies with maternal magnesium sulphate treatment

Results

In a group of 82 newborns (31-34 GA; birth body weight <1500 g) the umbilical cord serum magnesium concentrations was assayed. Three subgroups of neonates were set apart: first group (N) with a normal magnesium level (n=28), the second group (n=19) with magnesium concentration <0.75 mmol/dl (D), and the third group (Mg) consisting of 35 newborn antenatally exposed to magnesium sulphate. These groups were similar (no statistical significances) in terms of birth body weight, gestational age, Apgar score and umbilical blood pH. Gradual decrease in

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magnesium concentration in relation to increase of gestational age was observed. In groups: D, N, Mg, gradual reduction of hospitalization time ($p<0.05$), risk of death, time of respiratory support, time of oxygen therapy, rate of bronchopulmonary dysplasia, periventricular leucomalation ($p<0.05$) were observed respectively. Likewise, a rate of serious neurological complication (IVH/PVL) in group D was higher in comparison to groups N and Mg (although without statistical significances).

Conclusion

Our results confirm that umbilical cord magnesium concentration in VLBW neonates have an influence on neonatal outcome. Although it is premature to recommend ordering maternal magnesium sulphate treatment to improve neonatal outcome, in our opinion the data presented here should at least induce magnesium concentration monitoring in pregnant women and magnesium deficiency correction.

Key words: magnesium, preterm newborn, magnesium sulphate.

INTRODUCTION

Magnesium, which belongs to light metals, has been known for nearly 200 years. Many scientists, emphasizing its role played in a living organism and special function in many vital processes, call it "the element of life". Together with the development of civilization, food industry and agriculture, problems of magnesium deficiency and, as a consequence, its prophylactic and curative use, have become significant.

Magnesium has been widely used for many years as calcium antagonist in perinatology (as magnesium sulphate) for eclampsia and preeclampsia treatment and, with some limitations, as a tokolityc agent, too. Recently, some authors have emphasized a possible neuroprotective role of prenatnal magnesium administration in very low birth weight preemies (VLBW) (CROWTHER et al. 2003). Previously published studies also suggested that magnesium administered to pregnant women crosses the placenta barrier easily and very quickly, achieving high concentration in fetal blood as well as fetal brain. As a known antagonist of NMDA receptors (N-metylo D-asparagic acid) localized in the central nervous system, magnesium can prevent necrosis of neurons (MASON et al. 1996). It has also been revealed that maternal magnesium treatment produces beneficial effect on newborn condition after birth, assessed according to SNAP – *Score for Neonatal Acute Physiology* (DEERING et al 2005). The results of our last research on newborn delivered with symptoms of perinatal asphyxia indicate possible effect of magnesium on other membrane efectors (ZYLINSKA et al. 2002, GULCZYŃSKA et al. 2006).

The aim of the study is to find the correlation between umbilical serum cord magnesium concentration (normal or low) in a group of newborns without prenatal exposure to magnesium sulphate and their outcomes, as well as to compare their outcomes with antenatally MSO_4 exposed babies.

MATERIAL AND METHODS

The prospective study was conducted over two years period, between 2003 and 2005. The analysis involved 82 neonates delivered at the Research Institute of the Polish Mother's Memorial, who were admitted to the neonatal intensive care. The study group included neonates at the gestational age of 31 to 34 weeks and birth body weight <1500 g. Babies born with severe congenital malformation which could considerably influence neonatal outcome were excluded from this study.

The umbilical serum magnesium concentration was assayed in the neonates immediately after birth. Next, the neonates were divided in three groups based on whether or not they had been antenatally exposed to $MgSO_4$ as well as on the results of the umbilical serum magnesium concentration. The newborn babies without maternal magnesium sulphate treatment (control group) were divided to two groups: the first group a with normal magnesium level and the second group with the magnesium concentration below the normal range. Thus, three subgroups of neonates were set apart: first group (N) with normal magnesium level (n=28), the second group (n=19) with magnesium concentration <0,75 mmol/dl (D), and the third group (Mg) consisting of 35 newborn antenatally exposed to magnesium sulphate. The threshold values of a normal range of serum magnesium concentration were chosen according to referral values reported in neonatal literature (GOMELLA 1992).

The third group of neonates was allocated only because of antenatal exposure to magnesium, irrespective of the obtained serum magnesium level. This decision was made seeing that the assays performed just after birth could have reflected the maternal serum magnesium level occurred closely to the end of a drug infusion (*Cmax*), the lowest magnesium concentration noticed before beginning of the next infusion (*Cmin*) but also late drug elimination phase after completely finishing $MgSO_4$ therapy. In the group of 35 mother-infant pairs exposed to magnesium sulphate, the therapeutic indication to $MgSO_4$ was pregnancy induced hypertension (n=9), whereas for the others this drug was ordered as a tocolytic agent. The $MgSO_4$ in pregnant women was administered via continuous intravenous infusion in doses which depended on observed clinical effects: tocolysis or decrease of blood pressure (1–2 g /hour).

The mean dose of $MgSO_4$ given to pregnant women was 78.5 g (min. 2 g; max. 384 g). These infusions of $MgSO_4$ were continued for 1 to 17 days; (mean duration 4.6 days; median 2 days). The longest period between the end of a magnesium sulphate infusion to the time of childbirth was 18 hours.

The mean birth body weight of neonates in subgroup N was 1260 g (min. 550; max. 1500), mean gestational age was 30.93 weeks, and Apgar scores at 1^{st} and 5^{th} min. of life were 6.6 and 7.0 respectively. In subgroup D the same

variables were: BBW 1241g (min. 900; max. 1500), GA 31.21 weeks and mean Apgar score at 1st; 5th min of life were 6.84 and 7.05. Among neonates born by women treated prenatally with $MgSO_4$ the mean body weight was 1333 g (min. 820; max. 1500), mean gestational age 31.09 weeks, Apgar score at 1st and 5th min of life was 6.77 and 6.89 respectively (Figure1).

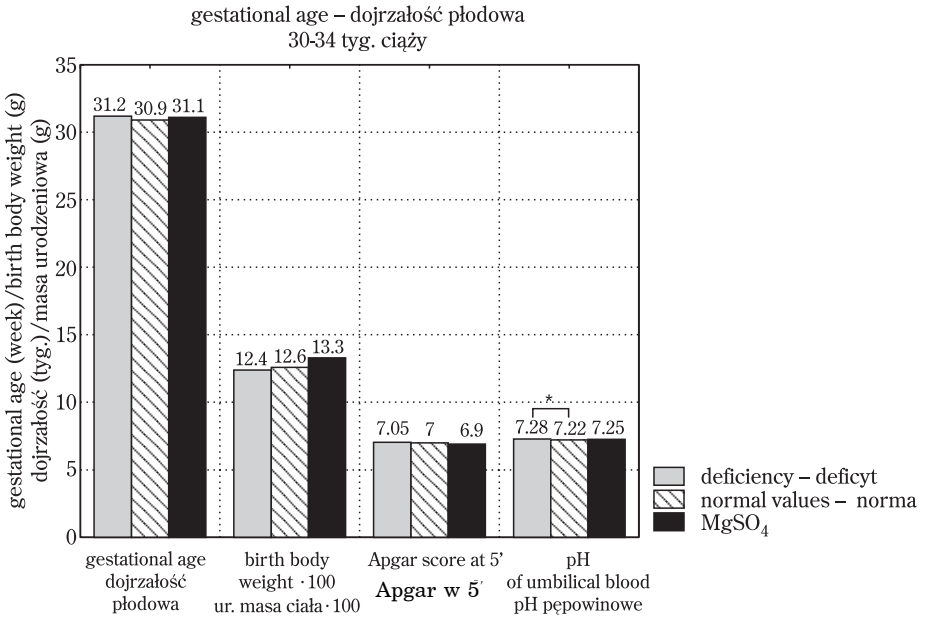

Fig. 1. The characteristic of studied groups of neonates
Rys. 1. Charakterystyka omawianych grup noworodków

The standard of VLBW neonate outcome involved: hospitalization time, risk of death, time of respiratory support, oxygen supplement time, rate of bronchopulmonary dysplasia diagnosed on 28th day of life as well as at 36 weeks of corrected age, rate of periventricular leucomalacia (PVL), severe intracranial hemorrhage (IVH III/IV grade) and its both combined index (PVL+IVH III/IV grade).

Determination of Mg in serum

The serum Mg level was determined colorimetrically (COBAS INTEGRA Roche Company) using chlorophosphonazo III.

RESULTS

Serum magnesium concentration was analyzed from cord blood immediately after delivery. In newborns with an antenatal maternal magnesium sulphate treat-

ment the mean magnesium concentrations were statistically significantly higher than in control subgroups N and D ($p<0.05$). It should be emphasized that the mean magnesium concentration was generally close to or slightly above the upper range of normal values (1.23 and 1.31 mmol/l), although in some of these newborns the serum magnesium concentration was still near the lower limit of a normal range (min; 0.71 mmol/l) – Table 1, Figure 2.

Table 1
Tabela 1

Magnesium concentrations assessed in umbilical cord serum
Stężenia magnezu stwierdzone w surowicy krwi pępowinowej

Mg serum concentratiom Stężenie Mg w surowicy krwi pępowinowej	30–34 tyg.c. (min–max)
Deficciency – Deficyt (D), <0,75 mmol/l) *n*=19	0.66 0.5–0.74
Normal values – Norma (*N*) *n*=28	0.83 0.75–0.99
$MgSO_4$ (Mg) *n*=35	1.31 0.71–2.46

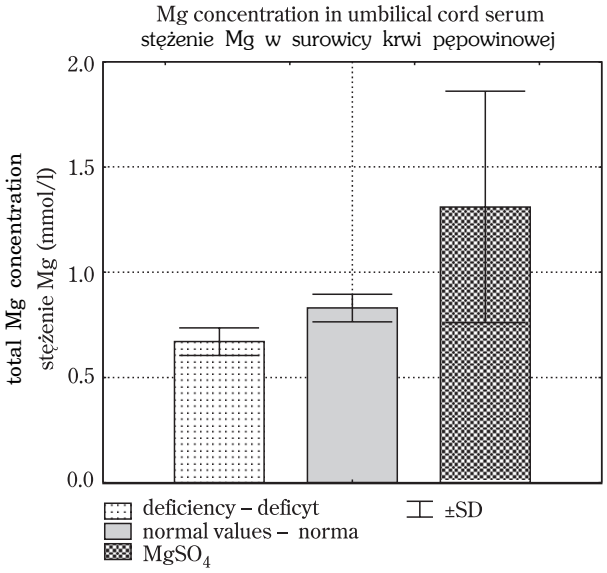

Fig. 2. Umbilical serum concentration in studied groups of neonates; mean values, SD
Rys. 2. Stężenie magnezu w surowicy krwi pępowinowej w badanych grupach noworodków; wartości średnie oraz SD

In the control group of newborns without prenatal exposition to magnesium sulphate, analyses of serum magnesium concentrations were taken on a group of 47 newborns. The results oscillated between 0.5-0.99 mmol/l. As many as 19 newborns (40%) had a serum magnesium concentration below the lower limit of norm (<0.75 mmol/l), and in 8 of them (17%) the levels were ≤0.65 mol/l. Simultaneously with the progression in gestation weeks, a decline in the cord blood serum magnesium concentration was observed (r=-0.25) – Figure 3.

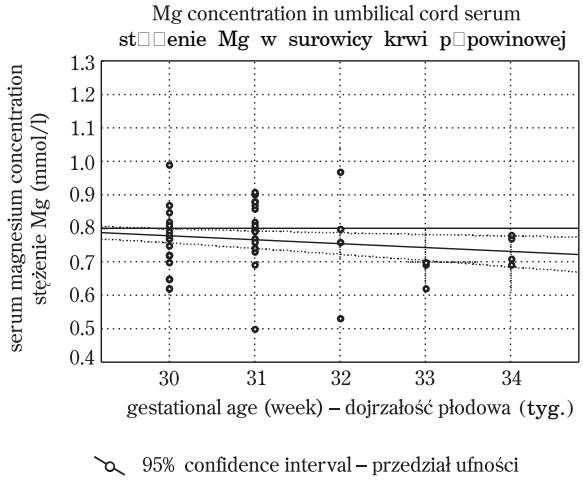

Fig. 3. Magnesium concentration variables in umbilical cord serum of control neonates according to increasing gestational age

Rys. 3. Zmiany stężenia magnezu w surowicy krwi pępowinowej noworodków z grupy kontrolnej wraz z narastaniem dojrzałości ciąży

Among the analyzed newborns, birth body weight as well as gestational age were comparable in particular subgroups (D; N; Mg). There were no statistically significant differences in subgroups. But the correlation between an increase in the magnesium concentration and an increase in body weight was observed. This correlation was visualized in each subgroup with a correlative chart of magnesium concentration and birth body weight (Figure 4). There were no gestational age differences in subgroups, which were similar in mean as well as median birth body weight (31 GA).

An analysis of outcomes shows a gradually shortening hospitalization time in consecutive subgroups (D; N; Mg). Statistically significant differences were observed between D, N, subgroups and Mg subgroup (p<0.05). There was one death in each group. Differences in percentage were dependent on the number of newborns in subgroups and were not statistically significant. Gradually shortening time of breathing support (in subgroups D – 5.73, N – 4.82, Mg – 4.29) and

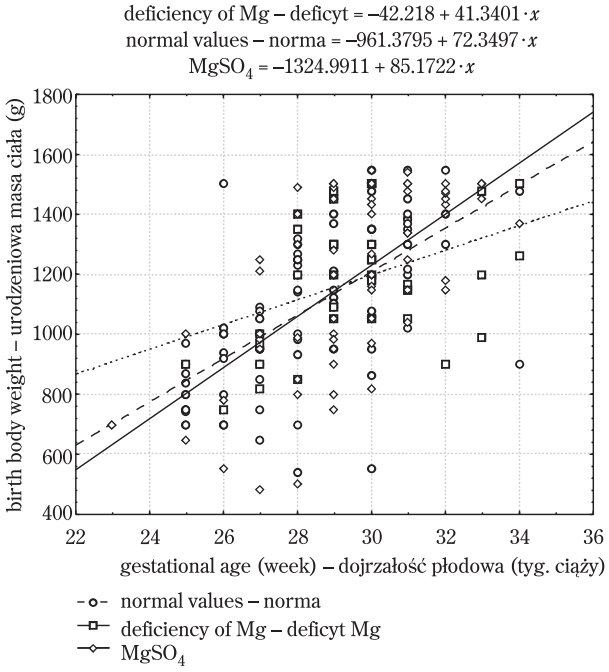

Fig. 4. The linear regression of birth body weight according to umbilical cord serum magnesium concentration

Rys. 4. Regresja liniowa urodzeniowej masy ciała w zależności od stężenia Mg w surowicy krwi pępowinowej

oxygen requirement (D – 10.74, N – 8.5, Mg – 7.66) without statistically significant differences was observed. There were variable results of frequency of bronchopulmonary dysplasia assessed on 28th day of life. This parameter was probably influenced by deaths in the first four weeks of life but a positive trend in subgroup Mg in contrast to subgroup D and N was observed. We did not recognize bronchopulmonary dysplasia in any subgroups in 36 week of postmenstrual age. Interestingly, increased frequency of periventricular leukomalacy among newborns with magnesium deficiency was observed. In this group PVL was recognized in 3 out of 19 newborns. In subgroup N no PVL was diagnosed, whereas in the subgroup treated with magnesium there were 2 recognized PVL out of 35 newborns (which gives D – 16%, N – 0%, Mg – 6%) – Figure 5.

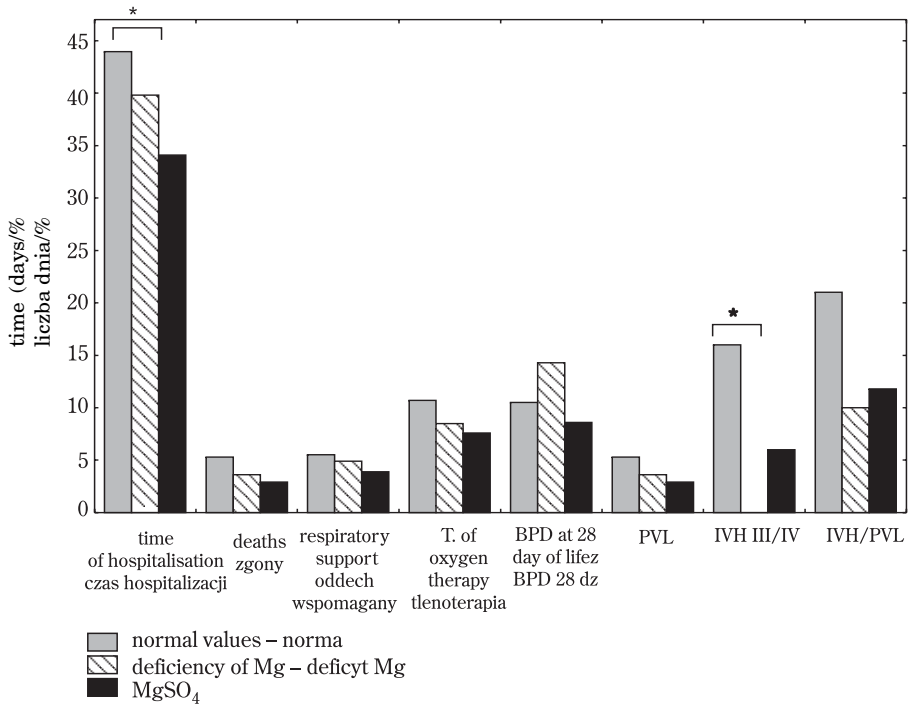

Fig. 5. Neonatal outcome in analyzed groups of preterm neonates
Rys. 5. Wyniki leczenia w okresie noworodkowym w analizowanych podgrupach noworodków

Explanation – Objaśnienia
BPD Broncho-Pulmonary Dysplasia – dysplazja oskrzelowo-płucna
CLD Chronic Lung Disease – przewlekła choroba płucna
cPVL cystic Periventricular Leucomalatia – torbielowata leukomalacja okołokomorowa
IVH Intraventricular Hemorrhage – krwawienie dokomorowe
NEC Necrotizing Enterocolitis – martwicze zapalenie jelit
PDA Persistent Ductus Arteriosus – przetrwały przewód tętniczy
RDS Respiratory Distress Syndrome – zespół zaburzeń oddychania
SIDS Sudden Infant Death Syndrome – zespół nagłej śmierci łóżeczkowej
SNAP Score for Neonatal Acute Physiology – ocena fizjologicznego stanu noworodka
VLBW Very Low Birth Weight – bardzo mała urodzeniowa masa ciała

DISCUSSION

Magnesium is a bioelment which has an important influence on health condition of the pregnant woman and her growing fetus. During pregnancy relatively low concentrations of this element are observed. Formation of new fetal tissues

and tissues of placenta lead to increased demand for magnesium. It was revealed that daily fetal retention of the amount of magnesium equals 10–18 mg. The comparison presented below shows the intensity of fetal absorption of Mg, Ca, P. A 175-gram fetus increases its body mass twenty-fold by delivery, whereas the contents of minerals (Mg, Ca, P) in the same period increase thirty to forty-five-fold (Dickerson et al. 1960, Widdowson et al. 1962).

The results confirm a negative correlation between the gestational age and magnesium concentration. Although assessment of the total serum magnesium concentration is not an optimal diagnostic method for magnesium deficiency, the results show depletion of magnesium concentration in many newborns (40%) without prenatal magnesium exposure. In 19% of them significant deficiency was diagnosed.

Linear regression chart of birth body weight in relation to gestational age shows the fastest increase in body mass in the prenatally $MgSO_4$ exposed subgroup and a slower gain in weight in the control subgroup with a low serum magnesium concentration.

Recently other authors have shown that the total as well as ionized magnesium serum concentration in pregnant women decreases with progression of gestation (Hurley et al. 1976, Durlach 2004, Marcus et al. 1998). The fluctuations observed can depend on hemodilution, which is caused by an increased amount of plasma during pregnancy, as well as increasing magnesium deficiency in pregnant women. It is also known that many women, especially those living under poor socioeconomic conditions, receive magnesium intake below daily recommended amount. Very young, adolescent women, multipara pregnant women and women in a consecutive pregnancy in a short time may be particularly prone to magnesium deficiency.

Despite analyzing variable subgroups of newborns and comparing magnesium exposed children with the control group (with normal and low magnesium concentration), the main objective of authors of this research was to assess dependency between the cord magnesium serum concentration and neonatal outcomes. It was speculated that the perinatal magnesium concentration could influence fetal/newborn reaction to a dynamic process of delivery, course of the adaptation period to extrauterine life and consequently late neonatal outcomes. Analysis of our results shows differences in frequency of such cerebral complications as: serious intracranial hemorrhages, periventricular leucomalacy and their combined rate. Despite the fact that this research did not reveal statistical differences in time of oxygen requirements, time of mechanical ventilation or frequency of bronchopulmonary dysplasia, the reduction of these parameters together with increased serum magnesium concentration was observed. The statistically significant differences in time of hospitalization were confirmed.

Deficiency of magnesium and other microelements during gestation can lead to a birth of a SGA child (Zigliara et al. 1973, Takaya et al. 2005). Nonetheless,

there are few publications in the current medical literature which concern influence of magnesium deficiency on a newborn's health condition. Research of some Philadelphian authors revealed that gestational magnesium deficiency could affect adversely not only on the course of a newborn period (increased risk of brochopulmonary dysplasia, respiratory distress syndrome, retinopathy of prematurity) (CADDELL 1993, 1995, CADELL et al. 1999) but can also be one of the elements of the multifactorial etiology of the sudden infant death syndrome (CADDELL 1996, CHIU et al. 2005).

The results of research on animals with experimentally induced magnesium deficiency show that it is an embriotoxic agent and influences fetal resorption, retardation of intrauterine growth, disturbances in skeletal development and skeletal malformations (GUNTHER 1981). Other animal models research revealed that magnesium deficiency, induced fourteen days before conception and lasting during pregnancy, led to reducing the number of offspring to 27% versus the control group. Because of death in the first eight hours of life, this percentage was reduced to 16%. The animals with induced magnesium deficiency had lower birth weight, a lot of superficial bleedings, intracranial bleedings and edemas of extremities. In a group with poor magnesium diet before conception but with adequate diet during gestation there was only a small reduction (to 86% in the number of offspring) and no other differences were observed. The results of this analysis seem to confirm the hypothesis that adequate supplementation of magnesium during pregnancy is necessary for fetal development and that post conceptional magnesium supplementation is beneficial for individuals living in magnesium poor environment.

There has been a long and heated discussion in perinatology about influence of prenatal $MgSO_4$ supplementation on results of preterms treatment. Both positive and negative effects were reported of tocolysis or treatment of pregnancy induced hypertension with magnesium sulphate. During $MgSO_4$ administration, an increased flow in uteral arteries along with the maintained normal flow in umbilical arteries of a fetus were observed (KEELEY et al. 1993). Simultaneously, a decreased diastolic flow in the middle cerebral artery of a fetal brain was noticed. Other authors using Doppler technique showed a two-fold increase in blood volume flowing through uteral arteries (from 5.09 ml/sek to 10.02 ml/sek) with a stable resistance index (SHAUF et al. 2004). This observation indicates that improvement in outcome of perinatal care could be related not only to anti-seizure properties of MgSO4, but also to improved saturation of fetal blood, which can be especially beneficial in pregnancies with a diagnosed intrauterine growth retardation syndrome.

Nowadays, after a period of criticism concerning efficacy and safety of tocolysis with $MgSO_4$, prenatal administration of magnesium sulphate is an interesting topic in the United States and Europe, owing to a possible neuroprotective activity of magnesium in a fetus and VLBW neonates. From the first publication by

Nelson K. and Grether J., who pointed out decreased frequency of cerebral palsy as an effect of prenatal exposure to MgSO4, other scientists have noticed beneficial influence of magnesium on neurological outcomes in very low birth weight newborns (Nelson et al. 1995). In the next years many centers of perinatology have conducted research into this subject, looking for correlation between magnesium supplementation and frequency of intracranial hemorrhage, PVL, deaths or cerebral palsy (Hirtz et al. 1998, Kuban et al. 1992).

In order to confirm neroprotective properties of magnesium sulphate administered to pregnant women with imminent preterm labor before the 30th week of gestation, Crowther and others organized a multicenter, randomized trial: Australasian Collaborative Trial of Magnesium Sulfate (ACTO$MgSO_4$) Collaborative Group (Crowther 2003). Research lasted from 1996 to 2000, and was conducted in 16 hospitals with the third referential level in Australia and New Zeeland. In total, 1062 pregnant women whose delivery was planned in 24 hours, were included in the trial. Total mortality of infants, frequency of cerebral palsy and combined index: death and/or cerebral palsy were analyzed at the age of 2. These negative neurological outcomes (as shown below) were less frequent in children who were treated with $MgSO_4$: mortality in infancy (13.8% vs 17.1%), cerebral palsy (6.8% vs 8.2%), combined index (19.8% vs 24.0%) but the differences were not statistically significant. Frequency of significant motor dysfunction was lower and this result was statistically significant (3.4 vs 6.6, RR: 0.51; 95% CI: 0.29–0.91). The same dependence occurred for combined index: death or significant motor dysfunction: (17% vs 22.7%; RR 0.75; 95% CI: 0.59–0.96).

Other authors from Europe reported a reducing influence of prenatal tocoloysys with magnesium sulphate combined with aminophyllin administration on risk of intracranial hemorrhage. (Di Renzo et al. 2005). There were four incidences of hemorrhage in the treated group (5.13%) vs 14 (20.6%) in the control. However, serious hemorrhage (IVH III and IV degree) was revealed in 1 (1.28%) vs 7 (10.3%) of newborns.

In the same year Japanese authors who analyzing perinatal risk factors of cystic form of periventricular leucomalacy (cPVL) emphasized the multifactorial etiology of this condition, suggesting that both maternal and fetal factors as well as administered drugs could play a role in development of PVL (Murata 2005). With multifactorial analysis, scientists proved that preeclamsia with prenatal $MgSO_4$ administration significantly reduced the risk of PVL. Harrison and colleagues proved higher frequency of hypoxic ischemic encephalopathy in newborns with symptoms of perinatal asphyxia and a low cord serum magnesium concentration than in newborns with perinatal asphyxia and the magnesium concentration in a normal range (Harrison et al. 1997). Many authors emphasize the fact that administration of $MgSO_4$ in doses lower than commonly used for tocolysys could have neuroprotective effect, without suggested risk of promoting lethal effect in extremely immature newborns.

Statistics concerning results of perinatal care show that about 50% of newborns with birth mass ≤1000 g who are alive on 28th day of their life develop symptoms of BPD. Simultaneously newborns with birth weight <1500 g (VLBW) run the risk of magnesium deficiency, which is connected with the fact that 80% of the total body magnesium is accumulated by a fetus in the third trimester of gestation. In 1996 CADDELL and others indicated the coincidence of magnesium deficiency and development of BPD. According to these authors, development of bronchopulmonary dysplasia could be provoked or exacerbated by magnesium deficiency (CADELL 1996). It is known that in pathogenesis of BPD the following are engaged: free oxygen radicals, proinflamatory cytokines (IL-1, IL-6), tumor necrosis factor-TNF-α, tromboxan A2 (TXA2), serotonin with it vasoconstrictive activity, endothelin-1 (ET-1) and histamine, which is a bronchospastic factor. It is proved that magnesium deficiency increases cell and tissue sensitivity to peroxydation, exacerbates inflammatory reaction, reduces immunologic answer, increases catecholamine output during stress and decreases energy metabolism (BUSS et al. 2002, WELTY et al. 2001)

CONCLUSION

The results of our study confirm the positive effect of an appropriate (i.e. within the normal range) fetal and newborn serum magnesium concentration (subgroup *N* vs *D*) on outcomes of VLBW neonates. Some of the observed parameters had improved after prenatal magnesium sulphate administration. This observation suggests a need for monitoring magnesium concentrations in pregnant women, removal of magnesium deficiency and possible improvement in outcomes with prenatal supplementation of magnesium sulphate. On the basis on our trial, in such cases it is extremely important to monitor the serum magnesium concentration in VLBV neonates and adequately calculate pre- and postnatal administration of this element.

Analyzing results from epidemiological studies, we still lack an answer to the question concerning optimal doses and time of magnesium administration, or the best magnesium compounds which should be used for supplementation or treatment.

Therefore, further, well-designed research into the effects of prenatal magnesium exposure and consequences of its deficiency on outcomes of pregnant women and their children is essential.

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