

# Correlation between antenatal magnesium sulfate (MgSO<sub>4</sub>) total dose and delivery time interval with umbilical cord blood brain-derived neurotrophic factor (BDNF) levels as a neuroprotection strategy in preterm birth

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## ABSTRACT

**Background:** Administration of antenatal magnesium sulfate (MgSO<sub>4</sub>) to pregnant women is thought to increase the synthesis of Brain-Derived Neurotrophic Factor (BDNF), which functions as a nerve-growth factor for the process of neurogenesis and also strengthen neuronal resilience in the hypoxic condition that occurs during preterm delivery. Protocols for administering antenatal MgSO<sub>4</sub> differ between countries and institutions. One of the concerns is whether the dose is given and the time interval to delivery has a big contribution towards a better fetal outcome. These relationships have not been studied before. This study aimed to analyze the correlation of the total dose of MgSO<sub>4</sub> and time interval to delivery with BDNF levels in cord blood.

**Methods:** This study enrolled 72 pregnant women who will deliver the baby prematurely, with gestational age 28-34 weeks. Subjects were divided into three protocols groups: (1) 4 g iv. only, (2) 4 g iv. initial continued with 1 g/hours until maximum 24 hours, and (3) 6 g iv. initial continued with 2 g/hours until a maximum of 24 hours. At the time of delivery, cord blood of preterm babies was collected. The antenatal MgSO<sub>4</sub> total dose and time interval to delivery were collected, and BDNF serum levels were then measured with enzyme-linked immunosorbent assay (ELISA). The correlation between antenatal MgSO<sub>4</sub> total dose and time interval to delivery with BDNF levels was analyzed using Spearman's correlation test.

**Result:** There was a weak significant correlation of antenatal MgSO<sub>4</sub> total dose and BDNF cord blood levels ( $p < 0.001$ ;  $r = 0.381$ ). There was no significant correlation between delivery time interval and BDNF cord blood levels ( $p = 0.44$ ;  $r = 0.092$ ).

**Conclusion:** Regarding the weak correlation of total dose and time interval to delivery with BDNF, we suggest that all protocols provide comparable outcomes if seen only from the BDNF increase perspective.

**Keywords:** Antenatal, BDNF, MgSO<sub>4</sub>, Preterm Birth.

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## INTRODUCTION

The incidence of preterm birth is still high even in developed countries and shows an increasing trend. The incidence of preterm birth in low-income countries is 12%, while in high-income countries is only 9%.<sup>1</sup> The incidence of preterm birth in Indonesia in 2010 was 15.5/100 live births and estimated having 675.700 preterm babies in total each year. These put Indonesia in the 5th rank of countries with the greatest numbers of preterm birth and the 9<sup>th</sup> rank position of countries with the highest rates of preterm birth per 100

live births in the world.<sup>1,2</sup>

Preterm birth gives infants a high risk of brain damage that can cause a long life disability such as cerebral palsy.<sup>3</sup> The more preterm, the more likely to get a brain injury. Antenatal neuroprotection strategy is necessarily important.<sup>3</sup> Antenatal magnesium sulfate (MgSO<sub>4</sub>) has recently been investigated as an effective neuroprotection strategy. It should be noted. However, there are varieties in protocols: 4 g only, 4 g continued by 1 g/h, and 6 g continued by 2 g/h.<sup>4-6</sup> It is interesting to know whether different protocols make a different outcome.<sup>7</sup>

One of the most prominent brain hormones is Brain-Derived Neurotrophic Factor (BDNF). Recent data suggest that one of the neuroprotection pathways of antenatal MgSO<sub>4</sub> is its pivotal role in triggering higher BDNF production in fetuses.<sup>8</sup> This hormone is believed to play a crucial part in neuronal defense mechanisms, which is extremely needed for premature babies to survive from brain injury related to prematurity. Prematurity is closely related to hypoxic-ischemic (H/I), leading to abnormal apoptosis of neurons and destruction of myelin. Brain-Derived Neurotrophic Factor is a potent

modulator capable of regulating a wide repertoire of neuronal functions. Evidence showed that BDNF was beneficial for the survival of neurons through anti-apoptotic effects by suppressing caspase-3 production and activation. BDNF may promote microglial proliferation and phagocytic activity in the inflammatory process via alteration of cytokines and chemokines production. Furthermore, BDNF mRNA accumulates in distal dendrites to block the binding between N-methyl-D-aspartate receptor (NMDAr) and glutamate, which is the primary causal of neuro-toxicity. On the other hand, BDNF also promotes neurogenesis, which involves cell proliferation, migration, and differentiation. It could facilitate regeneration among central and peripheral neurons after H/I damage to cerebral white matter, causing periventricular leucomalacia (PVL). Periventricular Leucomalacia is the main anatomical brain abnormality related to cerebral palsy.<sup>9,10</sup>

We primarily want to investigate the different protocols that make the total dose given different. This could make different levels of BDNF in prematurely born babies, which could explain which protocol is better. We also want to compare that analytical data with delivery time interval, should it falsely makes misinterpretation on total dose effect.

## MATERIALS AND METHODS

This study was designed as a cross sectional study and has received approval from the Ethical Committee of Dr. Moewardi General Hospital Surakarta (No 1.029/VIII/HREC/2020). We conducted the study from October 2020 until February 2021. We were carried out at the Obstetrics and Gynecology Department of Dr. Moewardi General Hospital Surakarta and Prodia Laboratory Jakarta for ELISA examination of umbilical cord blood BDNF.

The subjects of this study were pregnant women with inevitable spontaneous preterm labor or medically indicated preterm delivery (ranged 28-34 weeks of gestational age) who met inclusion and exclusion criteria and were willing to participate in the study and chose study group as her willing. Inclusion criteria were 20-35 years of age, 28-34 weeks

of gestation in an active phase of labor or planned for delivery due to medical reasons, and agreed to participate. Exclusion criteria were multiple pregnancies, intrauterine fetal death, a fetus with congenital abnormalities, born 3 hours after treatment started or more than 48 hours, and a prior history of MgSO<sub>4</sub> adverse events. The confounding factor, antenatal corticosteroid usage that is mandatory for fetal lung maturation in preterm birth, was taken into account and put on the statistical analysis.

According to the formula used, the number of subjects was 81, which has already put the extra number for drop-out. Patients were divided into three groups protocols (as existed in routine clinical protocols for fetal neuroprotection): (i) MgSO<sub>4</sub> iv. 4 g only (20 subjects); (ii) MgSO<sub>4</sub> iv. 4 g initial followed by 1 g/h for 24 hours (36 subjects); and (iii) MgSO<sub>4</sub> iv. 6 g initial followed by 2 g/h for 24 hours (16 people). Magnesium sulfate was given in 20% concentration and diluted using water for injection to provide 50 cc volume and given intravenously by syringe pump infusion to ensure the steady dose given each time. The total dose of MgSO<sub>4</sub> administered was limited to a minimum of 4 g and a maximum of 50 g. When the baby was delivered, either vaginally or abdominally, we took  $\pm 5$  cc of umbilical cord blood to examine BDNF levels. Cord blood samples were kept in the proper cold storage of Prodia Laboratory (-80 C) and were sent in cold-chain delivery to minimize the bias due to sample damage. Brain-Derived Neurotrophic Factor serum levels were examined quantitatively using ELISA with a microplate reader type 680 from Bio-Rad with quantikine human BDNF free immunoassay at Prodia Laboratory Jakarta. We also collected data for the total dose of antenatal MgSO<sub>4</sub> given for each subject; time interval to deliver, which is an hour from the provision of antenatal MgSO<sub>4</sub> started until the baby was born. Bias for the misinterpretation has been taken into account by duplicating the process using the same samples and re-read the results by the different analyst's staff.

In this study, univariate analysis was used to calculate the average maternal age, maternal body weight, gestational age, total

corticosteroid dose, maternal magnesium levels, umbilical cord blood magnesium levels, antenatal MgSO<sub>4</sub> total dose, and delivery time interval. Levene's test was used to analyze the homogeneity and Kolmogorov-Smirnov for the normality analysis of the data. Bivariate analysis with Spearman correlation analysis was used to calculate the study's primary outcome, which was the correlation between antenatal MgSO<sub>4</sub> total dose and umbilical cord blood BDNF levels; and the secondary outcome, which was the correlation between delivery time interval and umbilical cord blood BDNF levels. We also measured the association between the confounding factor, the doses of antenatal corticosteroid (dexamethasone) used with the umbilical cord BDNF levels. All of the analysis that resulted in  $p < 0.05$  was considered statistically significant. IBM SPSS® Statistics Ver.25 was used for all of the statistical analyses.

## RESULTS

This study enrolled 81 patients with purposive random sampling who met the inclusion and exclusion criteria and agreed to participate. There was no drop-out due to adverse events, nor refused to continue participation. There were four patients who gave birth spontaneously 3 hours after the treatment, and five patients had delivery after 48 hours of antenatal MgSO<sub>4</sub> administration and were discontinued from the ample collection. In the final, 72 patients were joining sample collection and data analysis. There were no missing data in this study. The characteristics of these subjects can be seen in [Table 1](#).

Characteristic of the subjects showed proper maternal age (29 years old), preterm gestational age (32 weeks) and proper body weight (64 kg). All subjects received dexamethasone as antenatal corticosteroids (14 mg). The maternal and fetal magnesium levels were 3.02 mg/dl and 2.98 mg/dl. Antenatal MgSO<sub>4</sub> total dose was 19 g and delivery time interval was 16 h, with fetal BDNF levels 11674.58 pg/ml.

The average maternal age was 29,83 $\pm$ 5,24 years, and the bodyweight was 64,26 $\pm$ 7,67 kg. The mean gestational age was 32,15 $\pm$ 2,01 weeks. The mean delivery time interval was 16,71 $\pm$ 9,30 h. All

patients received corticosteroid therapy (dexamethasone) as a mandatory protocol for lung maturation in preterm delivery, and the average dose given was  $14,03 \pm 5,91$  g. The total dose of  $MgSO_4$  administered was  $19,72 \pm 13,28$  g. The mean maternal magnesium levels were  $3,02 \pm 1,02$  mg/dl, while the mean umbilical cord magnesium levels were  $2,98 \pm 0,92$  mg/dl. The mean umbilical cord blood BDNF levels were  $11674,58 \pm 5074,74$  pg/ml. The mean baby birth weight was  $1696,81 \pm 423,98$  g.

Factors that could affect BDNF levels in the umbilical cord blood of premature babies are presented in Table 2, such as maternal magnesium levels and umbilical cord magnesium levels. The p-value was found to be significant for both factors. The total dose of antenatal  $MgSO_4$  was significantly correlated with maternal magnesium levels ( $r=0.448$ ,  $p<0.001$ ) and umbilical cord blood magnesium levels ( $r=0.294$ ,  $p=0.012$ ). Both were not

considered confounding factors since it is the direct and desired effect of the antenatal  $MgSO_4$  provision. Corticosteroid that is mandatory to be used for preterm birth protocol tends to impact the inclining production of BDNF, although statistically did not meet the criteria to be considered significant.

In addition, maternal magnesium levels were strongly correlated with umbilical cord magnesium ( $r=0.753$ ,  $p<0.001$ ). The total dose of antenatal  $MgSO_4$  seemed to significantly increase maternal and fetal magnesium levels, even though the effect was modest, as shown in Table 3. The study's primary and secondary outcome is shown in Table 4. The total dose of  $MgSO_4$  showed a significant weak effect to increase umbilical cord blood BDNF levels ( $r=0.381$ ,  $p<0.001$ ). There was no significant correlation between delivery time interval and umbilical cord blood BDNF levels ( $r=0.092$ ,  $p=0.440$ ).

Data distribution between the two variables is displayed in Linear Line form in Figures 1 and 2. As the primary outcome of this study, we can see a correlation between the antenatal  $MgSO_4$  total dose and cord blood BDNF levels was spread out following the existing fit line, as seen in Figure 1. This showed a positive linear relationship/correlation between the total dose of antenatal  $MgSO_4$  and cord blood BDNF serum levels in a weak fashion. Delivery time interval did not show a trend to correlate with the fetal BDNF level, as shown in Figure 2. It can be assumed that it did not falsely make a misinterpretation of the total dose effect.

## DISCUSSION

$MgSO_4$  has been investigated as effective neuroprotection in premature infants recently.<sup>3</sup> Antenatal administration of  $MgSO_4$  reduces infant mortality and the incidence of CP.<sup>7</sup> Protection of the immature brain in premature infants is an important challenge for obstetricians.<sup>7</sup> Babies born prematurely have been shown to have decreased gray and white matter cortex compared to term infants, which impacts long-term neurodevelopmental outcomes.<sup>11</sup>

Research on the administration of  $MgSO_4$  just before the baby was delivered prematurely for brain protection has been carried out widely in the last decade, as some solid evidence was found unexpectedly in the pre-eclampsia trial.<sup>12</sup> The BEAM (Beneficial Effects of Antenatal Magnesium Sulfate), PREMAG (Magnesium Sulfate Given before Very Preterm Birth), and ACTOMgSO<sub>4</sub> (Australasian Collaborative Trial of Magnesium Sulfate) studies have been carried out to evaluate the administration of magnesium sulfate as an emerging new possibility for effective brain protection for premature fetuses involving nearly 4,000

**Table 1. Characteristics of the subjects.**

Variable	Mean ± SD
Maternal age	29.83 ± 5.24
Maternal body weight (kg)	64.26 ± 7.67
Gestational age (weeks)	32.15 ± 2.01
Baby birth weight (g)	1696.81 ± 423.98
Corticosteroid total dose (mg)	14.03 ± 5.91
Maternal magnesium levels (mg/dl)	3.02 ± 1.02
Umbilical cord blood magnesium levels (mg/dl)	2.98 ± 0.92
$MgSO_4$ total dose (g)	19.72 ± 13.28
Delivery time interval (h)	16.71 ± 9.30
Umbilical cord blood BDNF levels (pg/ml)	11674.58 ± 5074.74

**Table 2. Factors affecting BDNF levels for preterm birth.**

Variable	p-value
Maternal magnesium (mg/dl)	0.002*
Umbilical cord blood magnesium (mg/dl)	0.022*
Corticosteroid total dose (mg)	0.061

Maternal and fetal magnesium levels showed a significant effect on BDNF production. \*Statistically significant result ( $p<0.05$ ).

**Table 3. Correlation of total  $MgSO_4$  with maternal and fetal magnesium levels.**

Variable	Total $MgSO_4$ (g)		Umbilical cord magnesium (mg/dl)	
	r	p value	r	p value
Maternal magnesium (mg/dl)	0.448	<0.001**	0.753	<0.001**
Umbilical cord magnesium (mg/dl)	0.294	0.0012*		

Spearman correlation test was used for the statistical analysis. The total dose of antenatal  $MgSO_4$  showed a weak correlation to maternal and fetal magnesium levels, and maternal magnesium levels showed a strong positive correlation to drive higher fetal magnesium levels. \*Statistically significant result ( $p<0.05$ ), \*\* Statistically significant result ( $p<0.01$ )

women, with the final results showing that the administration of magnesium sulfate in several different dosage variations has all been shown to reduce the incidence of cerebral palsy.<sup>6</sup> Following the results, guidelines worldwide for fetal neuroprotection in preterm delivery

came out, but in some varieties, including different protocols on antenatal MgSO<sub>4</sub> provision. The difference in protocols will cause different doses of antenatal MgSO<sub>4</sub> received. It is interesting to know whether this will affect different results in one of the most important hormones

in fetal neuroprotection, BDNF since the outcome of cerebral palsy rate and other neurological pathologic manifestation after birth were equal between different birth protocols.<sup>6</sup>

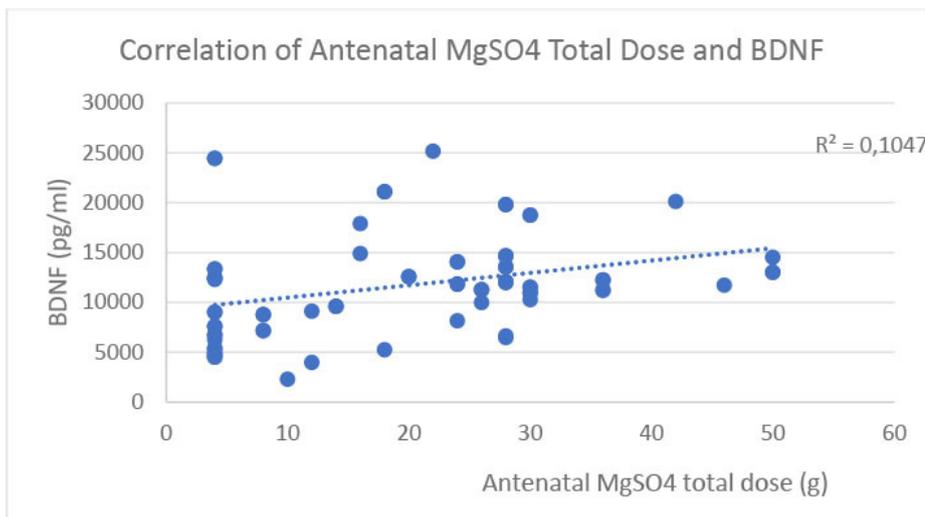
Assessment of the reduction in the risk of cerebral palsy in premature infants was associated with an increase in BDNF levels which was achieved as one of the expected effects after administration of MgSO<sub>4</sub>.<sup>8</sup> Administration of the MgSO<sub>4</sub> regimen will increase maternal blood magnesium levels, which will affect the production of BDNF in preterm infants to almost equivalent as term infants.<sup>8</sup> From Spearman's analysis in this study, antenatal MgSO<sub>4</sub> total dose showed only a weak positive correlation to umbilical cord blood BDNF levels, suggesting that all protocols will give similar not only in the clinical manifestation, also in the process of brain protection by the neurotrophic hormone itself. Delivery time interval describes the hours between an initial dose of antenatal MgSO<sub>4</sub> the baby is born. Spearman's analysis in this study showed no correlation between termination interval and BDNF levels. This is associated with the stable magnesium concentration in maternal blood at the time of administration of maintenance doses of antenatal MgSO<sub>4</sub> and the time of excretion of magnesium from the body. The previous study showed that after the initial dose, the serum magnesium level increased sharply to twice the threshold value in the first hour (3.59–4.13 mg/dl) and achieved a stable concentration (steady-state) after the second hour of administration. At the 8th, 12th, and 24th hours, magnesium serum levels remained stable and averaged 4.86 mg/dl. Magnesium levels will slowly decrease in 18 hours after the administration was ceased.<sup>13</sup>

The data above suggests that 4 g only, or 4 g followed by 1 g/h or 6 g followed by 2 g/h would result in almost similar maternal magnesium levels, and as the maternal magnesium levels are directly related to umbilical cord magnesium concentrations; it would make a comparable effect on the BDNF production in a fetus. Simchen et al., in their research, found a significant correlation between the increasing of maternal magnesium levels and the

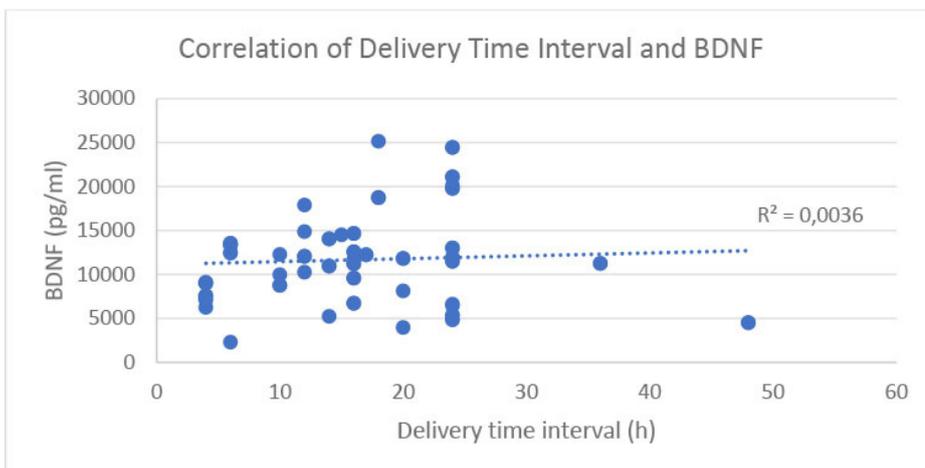
**Table 4. Correlation of total MgSO<sub>4</sub> and delivery time interval to BDNF.**

Variable	BDNF	
	r	p-value
Antenatal MgSO <sub>4</sub> total dose (g)	0.381	<0.001*
Delivery time interval (h)	0.092	0.44

Spearman correlation test was used for the statistical analysis. Antenatal MgSO<sub>4</sub> showed a weak positive correlation with increasing fetal BDNF levels, while delivery time interval did not. \*\*Statistically significant result (p<0.01).



**Figure 1.** Linear line correlation analysis of total MgSO<sub>4</sub> and umbilical cord BDNF levels. Positive trend on fetal BDNF levels increases due to total dose of antenatal MgSO<sub>4</sub>. However, the trend was weak.



**Figure 2.** Linear line correlation analysis of delivery time interval and umbilical cord blood BDNF levels. The flat line showed that delivery time interval did not affect higher fetal BDNF levels.

increasing of fetal magnesium levels after the administration of antenatal MgSO<sub>4</sub> in fetal neuroprotection strategy.<sup>14</sup> This is consistent with the results of this study, which found a relationship between the total dose of antenatal MgSO<sub>4</sub> and maternal magnesium levels ( $r=0.448$ ,  $p<0.001$ ) and umbilical cord blood magnesium levels ( $r=0.294$ ,  $p=0.012$ ). In addition, maternal magnesium levels were also strongly correlated with umbilical cord blood magnesium levels ( $r=0.753$ ,  $p=0.000$ ). The prior study explained that BDNF levels were higher in infants who received a complete dose of antenatal corticosteroids than infants who received partial corticosteroids.<sup>15</sup> In this study, the results found a similar trend but were still considered insignificant ( $p=0.061$ ). We still believe that dexamethasone administration before delivery in preterm birth as the mandatory protocol for lung maturation also influences fetal brain protection and has a good potentiation effect with antenatal MgSO<sub>4</sub> administered.

The limitation of this study was that we did not take the sample before the antenatal MgSO<sub>4</sub> provision. Pre- and post-treatment would theoretically give a better explanation of the increase of fetal BDNF production triggered by antenatal MgSO<sub>4</sub> administration. But, it is technically hard to do because to get samples from fetal blood before birth, we need to do cordocentesis. It is an invasive procedure with ultrasound guidance to make precise puncture on the umbilical cord and obtain the fetal blood. The number of subjects in this study was not enough to measure the cut-off point on which the total dose of antenatal MgSO<sub>4</sub> gave the highest fetal BDNF. We also need a study that focuses on the solitary effect of antenatal corticosteroids on BDNF production. We hope that there are more studies in the near future to discover the effective strategy of fetal brain protection for preterm delivery, as it has become one of the major priorities in modern obstetrics.

## CONCLUSION

All protocols exist in guidelines worldwide of antenatal MgSO<sub>4</sub> provision for

neuroprotection strategy in preterm birth gives almost comparable result on BDNF production. But as the world has already been familiar with 4 g initial continued with 1g/h maintenance, which is used in pre-eclampsia management protocols. It is probably the best choice for daily practice nowadays. However, 4 g only and 6 g followed with 2 g/h could still also be chosen, considering the administration easiness of the 4 g only, and the potential of a little bit higher fetal BDNF result in 6 g followed with 2g/h, resulting from higher MgSO<sub>4</sub> total dose.

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## DISCLOSURE

### Ethical Statement

This study has received approval from the Ethical Committee of Dr. Moewardi General Hospital Surakarta (No 1.029/VIII/HREC/2020).

### Patient's Consent

The study has fulfilled the patient's consent. Personal information about a patient will not be published. The patient had agreed that this study would use their data for statistical analysis, publication, and education purposes.

### Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper. The researchers also confirm their independence from funders and sponsors.

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## Authors contribution

All authors contributed equally to the study and the preparation of the manuscript.

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