# Antenatal Magnesium Sulfate for Neuroprotective Effects In Preterm Infants

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# 조산아에서 신경보호효과를 위한 산전 마그네슘 투여

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Fetal or neonatal brain injury can result in lifelong neurologic disability. Although survival rates for preterm infants have increased dramatically with the advent of modern perinatal and neonatal intensive care, but the rates of neurologic abnormalities in survivors, particularly motor disorders such as cerebral palsy, have not diminished. Antenatal magnesium sulfate may reduce the rates of cerebral palsy in survivors of preterm birth.

There are five randomized controlled trials of magnesium sulfate administered to women at risk of preterm delivery before 34 weeks of gestation which have reported neurological outcomes for the child.

From meta-analysis of these randomized trials, the rate of cerebral palsy was reduced by magnesium sulfate (RR, 0.69; 95% CI, 0.54-0.87; five trials; 6,145 infants) as did the moderate/severe cerebral palsy incidence (RR, 0.64; 95% CI, 0.44-0.92; three trials; 4387 infants). There was no statistically significant difference between the rates of neonatal adverse outcomes of the magnesium administration group and the control group. In most prospective randomized studies, no significant difference in the severe mother-side side effects between the magnesium sulfate administration group and the control group.

Antenatal magnesium sulfate therapy is neuroprotective against motor dysfunction in offspring for the preterm infant; however the possibility of an increase in the fetal or neonatal death rate was not completely excluded.

Key Words: Cerebral Palsy, Magnesium Sulfate, Mortality, Neroprotection, preterm birth

Perinatal brain injury can cause lifelong motor, sensory, and cognitive dysfunctions. Such brain damages are caused by cerebral ischemia, hemorrhage, infection, or injury. Preterm delivery is the most significant risk factor of neurological damages. Although survival rate for preterm infants has improved with advances in perinatal care over the past few decades, but the rates of neurologic abnormalities in survivors, particularly motor disorders such as cerebral palsy, have increased further, because infants who would previously have expired, now survive with their cerebral pathology.

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Despite the many efforts of the physicians, it is currently impossible to cure of cerebral palsy, its prevention is most important.

Magnesium sulfate has been used in obstetrics to prevent and treat convulsions in pregnancyinduced hypertension patients, and to inhibit uterine contraction in preterm labor patients.

Major medical organizations worldwide consistently recommend magnesium sulfate as a drug of choice for the prevention of eclampsia.<sup>1</sup>

The first report that prenatal magnesium sulphate was associated with a reduction in risk of IVH, was by Kuban and colleagues in 1992.<sup>2</sup> A significantly lower risk of IVH, from 18.9% to 4.4%, was found among babies born to mothers who had received magnesium sulphate regardless of whether they had preeclampsia.

In 1995, Grether and Nelson later described an association between antenatal magnesium sulphate and a reduced risk of cerebral palsy in VLBW infants (less than 1500 g). [odds ratio (OR), 0.14; 95% confidence interval (CI), 0.05-0.51].<sup>3</sup>

Since then, studies on the effects of magnesium sulfate on the development of cerebral palsy have been actively conducted. In 2002, Mittendorf et al. reported that the use of magnesium as a tocolytics in preterm labor was associated with worse, not better adverse outcomes such as neonatal intraventricular hemorrhage, periventricular leukomalacia, death and cerebral palsy in dose-response fasion.<sup>4</sup> According to Scudiero et al., the perinatal death rate of immature infants may increase when high-dose magnesium is used as tocolytics.<sup>5</sup> In some research results, whereas, the neonatal mortality rate did not associated with the use of antenatal magnesium administration.<sup>6,7</sup> In a study on very immature infants (less than 1,000 g), Kimberlin et al. analyzed the immature infant prognoses such as cerebral hemorrhage, convulsion, abnormal neurological findings, and the death rate according to the use of prenatal magnesium, and no specific association was confirmed. As described, the study results have not been consistent. In this prospective randomized controlled study, the effects of magnesium sulfate on the prevention of cerebral palsy were investigated.

# 1. Magnesium Sulfate for Neuroprotection in Animal Model

The neuroprotective effects of magnesium sulfate has been reported in many animal models of brain injury. In 1995, Marret et al. administered magnesium sulfate to mice with brain damages on the 5th day and the 10th day after their birth. They used excitotoxin disturbances during brain development in mice, by intracerebral injection of ibotenate, ecitotoxin from Muscaria, a kind of a mushroom., In this cerebral tocolytic arm experiment, ibotanated injected mice at 5 days after birth, white-matter damate accompanied by cystic change, similar periventricular leukmalacia in human was observed, whereas, no inhibition of a cerebral-infarction-like lesion was observed when magnesium sulfate was administered 10days after birth.8 Considering the various excitotoxin pathologies of mice according to their brain maturity stage, the neuroprotective effect of magnesium in humans may be most effective on the 26th to the 34th week of pregnancy, and the effect may be less in the full term.9 The neuroprotective effect of magnesium sulfate had also been reported in hypoxic-ischemic models. When seven-day-old mice with hypoxic-ischemic damage were administered magnesium sulfate, their apoptosis was reduced.<sup>10</sup>

# 2. Mechanism of the Neuroprotective Effects of Magnesium Sulfate

Temporary cerebral ischemia is known to cause per-

manent neural damages due to its reactions such as its release of excitatory neurotransmitters, the movement of calcium ions into the nerve cells, the formation of free radicals, lipid peroxidation, and protein dissolution.

Glutamate, a neurotransmitter, combines with the Nmethyl-D-aspartate (NMDA) receptor to abruptly increase the intracellular influx of calcium ions that promote the endonuclease functions, and eventually results in cell destruction.<sup>11</sup>

Although the change in the magnesium concentration cannot affect the recovery of the cell functions in their early stage, magnesium ions are antagonistic to calcium ions and play important roles in the physiological functions of normal nerve cells.<sup>12</sup>

The mechanism of the neuroprotective effect of magnesium sulfate is associated with the following in vivo functions of magnesium. First, magnesium reduces the synthesis of proinflammatory cytokines and free radicals to perform anti-inflammatory functions, and eventually decreases apoptosis.<sup>13</sup> Second, magnesium blocks the NMDA receptor to reduce the transfer of excitory stimuli.<sup>14</sup> Third, magnesium sulfate inhibits smooth muscle contractions to dilate the brain blood vessels and improve the cerebral blood flow, which decrease hypoxia and ischemic tissue damages.<sup>15</sup>

Due to these magnesium functions, neuroprotective effects are expected when magnesium sulfate is used.

## 3. Results of the Prospective Randomized Controlled Study

#### 1) The Magnesium and Neurological Endpoints Trial (MagNET) (1995-1997, USA)

In the MagNET trial,16 patients who had experienced preterm labor or premature rupture of their membranes on their 24th to 33rd week of pregnancy were assigned to either the group for the evaluation of the neuroprotective effects of magnesium sulfate (the neuroprotection arm) or the group for the evaluation of the uterine contraction (the tocolytic arm). When the uterine contraction (the tocolytic arm) group and the neuroprotective effect group were analyzed separately, no significant difference from the control group was observed. In the analysis of both groups together, the combined hazard ratio in the magnesium sulfate administration group was 32%, and in the placebo group, 19%, which showed no statistical significance (OR, 2.0; 95% CI, 0.99-4.1; P = 0.07), but the magnesium sulfate administration group. During the analysis of the infant death rate, the issue on the safety of magnesium sulfate administration was raised, and eventually, the study was terminated earlier than scheduled.

### 2) The Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO4) (1996-2000, Australia/New Zealand)

The ACTOMgSO4 trial<sup>17</sup> was a multi-institutional study conducted in 16 hospitals in Australia and New Zealand. Unlike the MagNET study, the infant death rate of the magnesium sulfate group did not increase (13.8% vs. 17.1%; RR, 0.83; 95% CI, 0.64-1.09; P = 0.19), and no significant difference in the rates of incidence of cerebral palsy was observed between the two groups, but the incidence tended to decrease in the magnesium sulfate group (6.8% vs. 8.2%; RR, 0.83; 95% CI, 0.54-1.27; P = 0.38), and the combined results of death or cerebral palsy showed a similar tendency (19.8% vs. 24.0%; RR, 0.83; 95% CI, 0.66-1.03; P = 0.09). In terms of the combined outcome of death or substantial motor dysfunction(17% vs. 22.7%; RR, 0.75; 95% CI, 0.59-0.96; P = 0.02), or substantial motor dysfunction as serious as being unable to walk independently until two years after birth(3.4% vs. 6.6%; RR, 0.51; 95% CI, 0.29-0.91; P = 0.02), the magnesium sulfate group showed a more statistically significant decrease than the placebo group did.

#### 3) PREMAG (1997-2003, France)

In the PREMAG trial,<sup>18</sup> which was a multi-institutional study conducted in France, enrolled 573 women less than 33 weeks of gestation who were expected to deliver within 24 hours. They received a single injection 4g loading dose of magnesium or isotonic 0.9% saline over 30 minutes, with no maintenance infusion.

Primarily, cases of severe white matter injury and infant mortality were analyzed. Two years later, the rates of infant mortality, cerebral palsy, and motor and cognitive impairments were analyzed during the follow-up period.<sup>19</sup> The protective effects of magnesium sulfate on cerebral palsy or death were found to have been significant (OR, 0.65; 95% CI, 0.42-1.03; P = 0.07) The decreases in the cerebral palsy and death rates, though statistically insignificant, were recognized as clinically important. In the magnesium sulfate group, the protective effects on severe motor disturbance or death were also confirmed (OR, 0.62; 95% CI, 0.41- 0.93; P = 0.02).

#### 4) The Beneficial Effects of the Antenatal Magnesium Sulfate (BEAM) Trial (1997-2004, USA)

In the BEAM trial,<sup>20</sup> 2,241 preterm delivery mothers on their 24th to 31st week of pregnancy who were expecting impending delivery were randomly assigned to the magnesium sulfate group or the placebo group in 20 US hospitals. In the cases of intermediate or severe cerebral palsy or death, no significant difference was observed between the magnesium sulfate group and the placebo group (11.3% vs. 11.7%; RR, 0.97; 95% CI, 0.77-1.23); but the incidence of moderate to severe cerebral palsy (1.9% vs. 3.5%; RR, 0.55; 95% CI, 0.32-0.95; P = 0.03) in the magnesium sulfate group significantly decreased. In both groups, no significant difference in the perinatal-period death rate was observed (9.5% vs. 8.5%; RR, 1.12; 95% CI0, 0.85- 1.47).

# 5) The Magnesium Sulfate for the Prevention of Eclampsia (Magpie) Trial (1998-2001, International)

The Magpie trial<sup>21</sup> was conducted to evaluate the preventive effects of magnesium sulfate on eclampsia. At the 18-month corrected age, the long-term effects of magnesium sulfate on fetuses were evaluated. No significant difference in the incidence rates of death or neurosensory disability (15.0% vs. 14.1%; RR, 1.06; 95% CI, 0.90-1.25), death (13.8% vs. 12.5%; RR, 1.11; 95% CI, 0.93-1.32), and sensory neural disturbance (1.3% vs. 1.9%; RR, 0.72; 95% CI, 0.40-1.29) was observed.

I summarizes the approximate summary of each study and the method of administration of magnesium sulfate in Table 1.

## 4. Meta-analysis

After the BEAM trial results were published in 2008, meta-analyses were conducted in five prospective randomized studies. According to the meta-analyses of women of gestational age less than 37 weeks, which was conducted in 2009, no overall significant difference in the pediatric mortality rates was confirmed (RR, 1.01; 95% CI, 0.82-1.23; five trials; 6,145infants).<sup>22-23</sup> (Table 2). However, the incidence of cerebral palsy decreased after the magnesium administration (RR, 0.69; 95% CI, 0.54-0.87; five trials; 6,145 infants), as did the moderate/severe cerebral palsy incidence (RR, 0.64; 95% CI, 0.44-0.92; three trials; 4387infants) (Table 3). There was no statistically significant difference between the rates of neonatal blindness, deafness, developmental retardation, and lower Apgar score at birth of the magnesium administration group and the control group<sup>23</sup>(Table 4). In addition, the risks of intraventricular hemorrhage, periventricular leukomalacia, and neonatal seizures, and the need for respiratory support, did not decrease<sup>24</sup> (Table 5). The same results were obtained in two groups of gestational age, less than 30

Study	Centers	Number of participants	Gestational age	Magnesium regimen	Neuroprotective outcomes
MagNET	1	149 mothers	25-33 weeks	4 gm bolus	Antenatal MgSO4 was associated with worse perinatal
Mittendorff et al	(United States)	165 fetuses		(neuroprotective arm)	outcome
ACTOMgSO4,	16	1,062 mothers	<30 weeks	4 gm bolus, 1 gm/h	CP RR:0.83; 95% CI: 0.54-1.27
Crowther et al	(Austrailia and New Zealand)	1,255 fetuses		maintenance	
PreMAG trial + follow-up trial, Marret et al	18 (France)	573 mothers 688 fetuses (original trial) 472 children (follow-up trial)	<33 weeks	4 gm bolus, no maintenance	Original trial: Nonsignificant decrease in risk of short-term severe white matter injury, mortality before hospital discharge Follow-up trial (2 years): Combined death or cerebral palsy OR: 0.65; 95% CI: 0.42-1.03
BEAM, Rouse et al	20 (United States)	2,241 mothers 2,444 fetuses	24-31 weeks	6 gm bolus, 2gm/h maintenance	Combined death or gross motor dysfunction OR: 0.62; 95% CI: 0.41-0.93 (statistically significant) Significant decrease in the risk of moderate or severe CP (RR: 0.55: 95% CI: 0.32-0.92) among survival children in the MgSO <sub>4</sub> group Death and CP RR: 0.97; 95% CI: 0.77-1.23
Magpie trial, Duley et al	125 (International)	3,283 children	<37 weeks c preeclampsia	4 gm bolus, 1 gm/h IV maintenance or, 4 gm bolus combined with 10 gm IM, then 5 gm/4 hrs IM maintenance	Combined death or neurosensory disability RR: 1.06; 95% CI: 0.40-1.29

Table 1. Characteristics o	f	Includ	led	l Studies
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CI: Confidence Interval; CP: Cerebral Palsy; OR: Odds ratio; RR: Relative risk

Table 2. Meta-Analysis of Mortality, Cerebral Palsy, Substantial Gross Motor Dysfunction an Combined Outcome by Subcategory of Intent<sup>23</sup>

Outcome and Subcategory	No. of Studies	Magnesium n/N (%)	Control n/N (%)	RR*	95% CI*	Statistical Significance	Heterogeneity [l <sup>2</sup> (%)]
Mortality							
Neuroprotective intent	4	226/2,199 (10.3)	242/2,247 (10.8)	0.94	0.77-1.15	Z=0.58, P=.56	19.6
Other intent	2	217/853 (25.4)	188/846 (22.2)	2.86	0.23-35.8	Z=0.81, P=.42	71.2
Total	5'	443/3,052 (14.5)	430/3,093 (13.9)	1.01	0.82-1.23	Z=0.08, P=.94	44.9
Cerebral palsy		RC 03 4.25	18 18 US				
Neuroprotective intent	4	102/2,199 (4.6)	146/2,247 (6.5)	0.71	0.55-0.91	Z=2.74, P=.006	25.2
Other intent	1	2/853 (0.2)	8/846 (0.9)	0.29	0.07-1.16	Z=1.75, P=.08	0
Total	5'	104/3,052 (3.4)	154/3,093 (5.0)	0.69	0.54-0.87	Z=3.07, P=.002	11.7
Mortality or cerebral palsy							
Neuroprotective intent	4	328/2,199 (14.9)	387/2,247 (17.2)	0.85	0.74-0.98	Z=2.21, P=.03	5.3
Other intent	2	219/853 (25.7)	196/846 (23.2)	1.28	0.68-1.12	Z=0.75, P=.45	36.5
Total	51	547/3,052 (17.9)	583/3,093 (18.8)	0.94	0.78-1.12	Z=0.70, P=.48	51.3
Substantial gross motordysf	unction						
Neuroprotective intent	3	56/2,169 (2.6)	94/2,218 (4.2)	0.60	0.43-0.83	Z=3.08, P=.002	0
Other intent	1	1/798 (0.1)	0/795 (0)	2.99	0.12-73.3	Z=0.67, P=.50	NA
Total	4	57/2,967 (1.9)	94/3,013 (3.1)	0.61	0.44-0.85	Z=2.98, P=.003	0
Mortality or substantial gros	s						
motor dysfunction							
Neuroprotective intent	3	280/2,169 (12.9)	335/2,218 (15.1)	0.84	0.71-1.00	Z=1.95, P=.05	25.2
Other intent	1	210/798 (26.3)	188/795 (23.6)	1.11	0.94-1.32	Z=1.23, P=.22	NA
Total	4	490/2,967 (16.5)	523/3,013 (17.4)	0.92	0.75-1.12	Z=0.87, P=.39	65.0

RR, relative risk; CI, confidence interval; NA, not applicable. \* Values obtained from meta-analysis, which is not obtained simply by comparing pooled rates of events. † One study4 represented in both subgroups; hence, there are only five studies overall.

Table 3. Effect of	f magnesium	sulfate on	cerebral	palsy	y and	pediatric	2 mortality <sup>2</sup>	4
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		No. of events/tota	l number		
Outcome	No. of trials	Magnesium	No magnesium	Relative risk (95% CI)	I <sup>2</sup> (%)
Cerebral palsy	6	104/2658	152/2699	0.69 (0.55-0.88)	4.4
Moderate/severe cerebral palsy	3	45/2169	72/2218	0.64 (0.44-0.92)	0.0
Mild cerebral palsy	3	54/2169	74/2218	0.74 (0.52-1.04)	0.0
Total pediatric mortality	6	401/2658	400/2699	1.01 (0.89-1.14)	38.9
Fetal mortality	5	17/2254	22/2298	0.78 (0.42-1.46)	0.0
Under 2 y of corrected age mortality	5	217/2254	220/2298	1.00 (0.84-1.19)	47.3
Death or cerebral palsy	6	505/2658	551/2699	0.92 (0.83-1.02)	43.3

CI, confidence interval.

Table 4. M	eta-Analysis	of Other	Neurologic	Outcomes <sup>23</sup>

Outcome	No. of studies	Magnesium [n/N (%)]	Control [n/N (%)]	RR (95% CI)*	Statistical Significance	Heterogeneity [I <sup>2</sup> (%)]
Newborn period	11 m - 1				1711	St 18 1940 - 3 1949
Apgar less than 7 at 5 minutes	3	351/2,169 (16.2)	351/2,218 (15.8)	1.03 (0.90-1.18)	Z=0.42, P=.68	7
Ongoing respiratory support	3	980/2,169 (45.2)	1,069/2,218 (48.2)	0.94 (0.89-1.00)	Z=1.91, P=.06	24
Any intraventricular hemorrhage	4	467/2,254 (20.7)	493/2,298 (21.5)	0.96 (0.86-1.08)	Z=0.65, P=.51	20
Periventricular leukomalacia	4	71/2,254 (3.1)	76/2,298 (3.3)	0.93 (0.68-1.28)	Z=0.43, P=.67	0
Neonatal convulsions	3	55/2,169 (2.5)	70/2,218 (3.2)	0.80 (0.56-1.13)	Z=1.28, P=.20	0
Follow-up						
Blindness	3	3/1,779 (0.2)	4/1,757 (0.2)	0.74 (0.17-3.30)	Z=0.40, P=.69	0
Deafness	3	9/1,779 (0.5)	12/1,757 (0.7)	0.79 (0.24-2.56)	Z=0.40, P=.69	17
Developmental delay	4	647/2,967 (21.8)	670/3,013 (22.2)	0.99 (0.91–1.09)	Z=0.11, P=.91	0

RR, relative risk; CI, confidence interval.

\* Values obtained from meta-analysis, which is not obtained simply by comparing pooled rates of events.

Table 5. Effect of magnesium sulfate on neonatal outcomes<sup>34</sup>

		No. of events/f	otal number			
Outcome	No. of trials	Magnesium	No magnesium	Relative risk (95% CI)	I <sup>2</sup> (%)	
Intraventricular hemorrhage (all grades)	5	467/2254	493/2298	0.96 (0.86-1.08)	20.1	
Grade III/IV intraventricular hemorrhage	4	74/1902	91/1962	0.83 (0.61-1.11)	0.0	
Periventricular leukomalacia	5	71/2254	76/2298	0.93 (0.68-1.28)	0.0	
Apgar score < 7 at 5 min	3	351/2169	351/2218	1.03 (0.90-1.18)	7.3	
Neonatal seizures	3	55/2169	70/2218	0.80 (0.56-1.13)	0	
Respiratory distress syndrome	2	730/1540	779/1592	1.01 (0.85-1.19)	65.8	
Need for supplemental oxygen at 36wk	2	220/981	195/962	1.12 (0.95-1.32)	23.1	
Bronchopulmonary dysplasia	1	213/1188	218/1256	1.03 (0.87-1.23)	NA	
Mechanical ventilation	3	1381/2169	1446/2218	0.99 (0.89-1.09)	82.1	
Necrotizing enterocolitis	3	155/2169	131/2218	1.23 (0.98-1.54)	0.0	

CI, confidence interval; NA, not applicable.

Table 6. Effect of magnesium sulfate on maternal outcomes<sup>24</sup>

		No. of events	/total number			
Outcome	No. of trials	Magnesium	No magnesium	Relative risk (95% CI)	I <sup>2</sup> (%)	
Death	3	0/1917	1/1950	0.32 (0.01-7.92)	0.0	
Cardiac or respiratory arrest	3	0/1917	35 0/1950	Not estimable	NA	
Pulmonary edema	1	8/1096	3/1145	2.79 (0.74-10.47)	NA	
Respiratory depression	2	41/1631	31/1672	1.31 (0.83-2.07)	0.0	
Hypotension	2	80/821	52/805	1.51 (1.09-2.09)	3.6	
Tachycardia	1	56/535	36/527	1.53 (1.03-2.29)	NA	
Severe postpartum hemorrhage	2	28/821	26/805	1.06 (0.63-1.79)	0.0	
Cesarean section	3	822/1917	834/1950	1.00 (0.93-1.07)	21.6	
Clinical and self-assessed maternal side effects of						
the infusion						
Flushing	3	1119/1917	162/1950	7.56 (3.39-16.88)	93.8	
Nausea or vomiting	3	312/1917	76/1950	4.60 (1.54-13.75)	91.5	
Sweating	2	411/1631	57/1672	6.37 (1.96-20.68)	94.6	
Problems at injection site	2	614/1631	68/1672	9.12 (7.19-11.57)	0.0	
Stopping of infusion because of adverse effects	2	123/1631	44/1672	2.81 (2.01-3.93)	0.0	
Any side effect	3	1356/1917	343/1950	5.05 (2.06-12.39)	98.3	

CI, confidence interval; NA, not applicable.

weeks(3,107 subjects) versus 32 to 34 weeks(5,235 subjects). The effects of the magnesium administration on the preterm delivered earlier than the 34th week were not significant.<sup>24</sup>

# 5. Side Effects of Magnesium Sulfate

The maternal outcomes of magnesium, including flush, sweating, nausea, vomiting, and pain in the in-

jection site is mild. Severe side effects of excessive administration include deterioration of respiratory functions due to breathing-muscle paralysis. Cardiac arrest or death may occur, but in most prospective randomized studies, no significant difference in the severe mother-side side effects such as cardiac arrest and death was observed between the magnesium sulfate administration group and the control group. In the magnesium administration group, the administration was often interrupted due to the side effects(Table 6). Regarding the neonatal death rate, the MagNET trial reported a higher rate in the magnesium sulfate administration group than in the control group. Since then, however, all the studies confirmed no increase in the death rate.<sup>16-18,20-21</sup>

In 2013, the US FDA recommended that pregnant women not be administered magnesium for longer than five to seven days because of the risk of hypermagnesemia and hypocalcemia that can induce bone problems, including fracture. This recommendation was based on many case study results, not on long-term monitoring. However, the US FDA announced that the use of magnesium sulfate as a preterm-labor treatment agent would be prohibited, and its deformity risk grade would be changed from Grade A to Grade D.<sup>25-26</sup>

#### 6. Conclusion

The results of previous studies have shown that the administration of magnesium sulfate to women expecting imminent preterm birth has neuroprotective effects. In the case of women at risk of preterm delivery, magnesium sulfate is necessary for neuroprotective purposes.

When magnesium sulfate was administered to women who were expecting a preterm birth within 24 hours, the risk of cerebral palsy or severe motor dysfunction was reduced, but the possibility of an increase in the fetal or neonatal death rate was not completely excluded.

- Magnesium sulfate can be used on the verge of delivery for preterm delivery cases with preterm premature rupture of membranes or intact membrane, an indications of preterm delivery.
- The neuroprotective effect of magnesium sulfate is limited to the gestation age range of 24-32 weeks.
- When magnesium sulfate is used for neuroprotection, its loading dose is 4 g, which is instilled for 20 minutes, and its maintenance dose is 1 g per hour. Its administration must be stopped when delivery does not occur within 24 hours.

Considering the risks involved in magnesium sulfate administration, its retreatment have to be avoided after initial course of magnesium sulfate therapy, when delivery is delayed. Since magnesium penetrates the placenta well, it is detected in the fetal blood within one hour after its administration, and in the amniotic fluid, within three hours. Further studies on the appropriate magnesium sulfate administration dose and period and its repeated administration may be needed in the future.

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#### Peer Reviewers' Commentary

Fetal or neonatal brain injury can result in lifelong neurologic disability. Although survival rate for preterm infants have increased dramatically with the advent of modern perinatal and neonatal intensive care, but the rates of neurological abnormalities in survivors, particularly motor disorders such as cerebral palsy, have not diminished. Antenatal magnesium sulfate therapy is neuroprotective against motor dysfunction in offspring for the preterm infant; however the possibility of an increase in the fatal or neonatal death rate was not completely excluded. In this review, summarized the recent study of magnesium for the neuroprotective effect of prematurity, which was to be used more useful clinically.