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Effect of magnesium sulphate for antenatal mothers in preterm labour for neuroprotection in infants

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Abstract
Background and Aim: In recent times, survival of preterm infants has improved drastically. In addition to significant contribution to neonatal mortality, impact of prematurity among survivors may continue throughout life impairing long-term physical life through neuro-disability. Maternal administration of magnesium sulphate prior to impending preterm birth is an effective strategy to reduce neuromorbidity. Hence, the present study aimed to investigate the effectiveness of antenatal magnesium sulphate for neuroprotection in preterm infants between 26 and 34 weeks in preventing early neonatal morbidity and mortality. Secondary objective was to assess any adverse events with the use of magnesium sulphate on the mother and neonate.
Materials and Methods: This was a prospective observational study at our tertiary care hospital of 50 pregnant women who gave preterm births. Fifty infants each were born to mothers who were given 4gm intravenous loading dose MgSO4, preferably 4 h prior to preterm birth.
Results: Among all the preterm in our study, 90% delivered between 30 and 34 weeks. Thompson score revealed that 60 % of the new-born had normal neuronal development.Considering infusion ($MgSO_4$) – delivery interval, 80% of delivery occurring after 13 hours was predominant. The APGAR score at 1 minute was 5.78±1.64 and at 5 minutes 7.44±1.49 was observed. About 92% of the neonates were normal.
Conclusion: Antenatal magnesium sulphate given to women in established preterm labour conferred significant neuroprotective advantage to the neonate and it is a safe drug to use in antenatal women.

Keywords: Preterm, neuroprotection, magnesium sulphate, neonates, thompson score

Introduction
Every year, almost 15 million babies are born preterm (before 37 weeks of pregnancy), accounting for 11% of all births worldwide [1]. Babies born preterm have fragile brains and are more likely to die early in life than those born full term [2, 3]. Preterm babies who survive are more likely to develop neurologic abnormalities such as cerebral palsy, blindness, deafness, or cognitive dysfunction, putting them at a higher risk of significant handicap [4]. The earlier the pregnancy, the higher the risk for baby at the time of birth. According to estimates, up to 8% of preterm neonates suffer neurological deficits, with 5% having mild impairments and 3% having significant or severe impairments [5]. The most common causes of neurological impairment are cerebral palsy and cognitive dysfunction, such as intellectual impairment or developmental delay. More newborns are at risk of dying and, among those who survive, have a risk of negative neurological outcome. As the rate of preterm delivery rises in many nations, there is a significant strain on the global economy [6]. Effective therapy for preterm survival that can lower the likelihood of neurological abnormalities and disabilities are desperately needed.
Premature baby survival has grown dramatically as a result of improved prenatal and neonatal care. Premature newborns who survive, on the other hand, place a significant burden on families, society, and the healthcare system. Respiratory and cardiovascular problems, cerebral bleeding, necrotizing enterocolitis, hypothermia, and NICU stays are all short-term complications of premature birth. Those who overcome these initial challenges may develop intellectual disabilities, cognitive dysfunction, hearing and vision impairments in the long run. These problems rise in direct proportion to lower gestational age at birth, lower birthweight, and inferior medical care facility quality [7]. Not only can appropriate neonatal care reduce perinatal morbidity and death, but so can prompt therapies given to the mother in the form of prenatal steroids, antibiotics, and $MgSO_4$ for enhancing lung maturity, susceptibility to infections, and neuroprotection, respectively [8].

The specific mechanism of magnesium sulphate's ($MgSO_4$) participation in embryonic brain neuronal damage prevention is unknown. Intracellular glycolysis, oxidative phosphorylation, protein synthesis, and cell membrane integrity all require magnesium ions. Following hypoxic ischemia and reperfusion, magnesium appears to inhibit the production of pro-inflammatory cytokines and free radicals while also preventing calcium-induced damage.

$MgSO_4$ has long been utilized as a tocolytic drug in preterm labour and to avoid seizures in patients with pre-eclampsia. In a case–control study of extremely low-birth weight infants in 1995, Nelson and Grether were the first to report that there was a relationship between the occurrence of cerebral palsy and exposure to $MgSO_4$. When all other factors were held constant, it was discovered that newborns exposed to $MgSO_4$ during pregnancy were less likely to develop cerebral palsy than those who were not [9]. Since then, three randomized trials have been conducted to assess the efficacy of $MgSO_4$ in preventing neonatal mortality, perinatal cerebral injury, and cerebral palsy in premature births, one each in Australia and New Zealand (Australia Collaborative Trial of the $MgSO_4$ group/ ACTOMAG), France (PREMAG), and the United States (Beneficial effect of antenatal magnesium sulphate / BEAMS) [10-12]. Its neuroprotective effect was later verified in 2009 by a meta-analysis of all known clinical trials [13, 14]. In the same year, a Cochrane study suggested using $MgSO_4$ for neuroprotection when the baby is due before 32 weeks of pregnancy [15].

Despite the fact that the goal of all three randomized trials was to assess the effect of magnesium sulphate on neurodevelopmental outcomes and mortality in preterm neonates, comparisons between trials are difficult due to differences in the populations studied, gestational age at treatment, inclusion and exclusion criteria, $MgSO_4$ regimes, and outcome variables assessed. $MgSO_4$ infusions have ranged from 4 gm in 15 minutes to 6 gm in 20 minutes, with maintenance doses ranging from none to 3 gm/hour and infusion times ranging from 12 to 24 hours. On the contrary, early outcomes in preterm infants treated with $MgSO_4$ for neuroprotective purposes have shown an increased risk of intra ventricular haemorrhage, impaired intestinal blood flow in the hours after birth, increased spontaneous bowel perforation, increased neonatal intensive care admissions, and the need for intubation in a small number of studies [16].

Our aim was to evaluate the effects of $MgSO_4$ on neurodevelopmental outcomes and death of the infants born to antenatal mothers at risk of preterm birth from 28-34 weeks of gestation.

Recommended Treatment protocol

- Magnesium sulphate: 4gm i.v loading dose over 20 minutes followed by 1 gram i.v per hour for atleast 24 hours or until delivery. After 24 hours, unless delivery is anticipated the infusion should be stopped.
- Magnesium sulphate: 4gm i.v loading dose over 20 minutes followed by 2 grams i.v per hour for atleast 12 hours or until delivery. After 12 hours, unless delivery is anticipated the infusion should be stopped.

Materials and methods

It was a prospective observational study done at Rajah Muthiah Medical College & Hospital, Chidambaram from October 2019 to October 2021 at our tertiary care referral hospital of pregnant women who gave preterm births between 28 and 34 weeks either due to spontaneous preterm labour and/or planned preterm birth for foetal or maternal indications. Fifty pregnant women were recruited in the present study

Inclusion Criteria

- All pregnant women of gestational age 28-34 weeks in labour.
- All pregnant women of gestational age 28-34 weeks anticipated to deliver in next 24 hours.

Exclusion Criteria

- Pregnant women with renal disease and liver disease
- Myasthenia Gravis
- Mitochondrial myopathy
- Diabetes Mellitus
- Patient refusal

Data Collection

The cases in study were diagnosed after clinical examination was done. The study group which consists of 50 preterm pregnant women lesser than 34 weeks gestation who were given magnesium sulphate as to colysis. Maternal parameters such as respiratory rate, urine output, deep tendon reflexes, blood pressure and pulse rate were monitored. Perinatal outcome for neuro protection, perinatal death and seizures were observed.

Results

Baseline characteristics of newborn

The mean birth weight of new-born was1.76±0.39 kg and ranged from 0.7 to 2.5 kg (Table 1). The newborn gender showed that male was predominant (56 %) and female was 44%.

Table 1: Baseline characteristics of new-born

Variables	Mean±SD/Frequency	
Baby weight in kg	1.76±0.39	
Baby gender (M:F)	28:22	56:44

Obstetric score

Among the study population, primi gravida was the major obstetric status (42%) followed by G2P1L1 (24 %) (Table 2). The G2A1 was observed in 14 %, G3P2L2, G3P2L1, G4P2L2A1 and G3P1L1A1were observed in 4 % each (Fig.1).

Table 2: Obstetric status of study participants

Score	Frequency	%
Primigravida	21	42
G2P1L1	12	24
G2A1	7	14
G3P2L2	2	4
G3P2L1	2	4
G4P2L2A1	2	4
G3P1L1A1	2	4
G5P4L4	1	2
G3P2L1	1	2

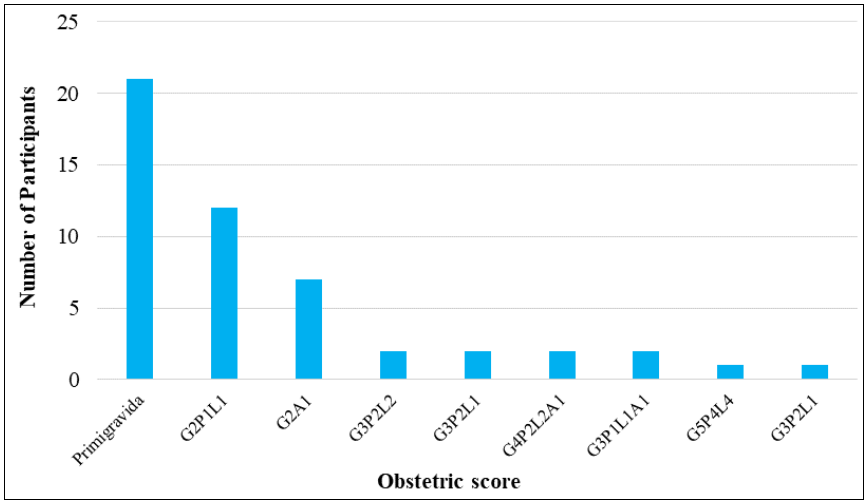


Fig 1: Obstetric score

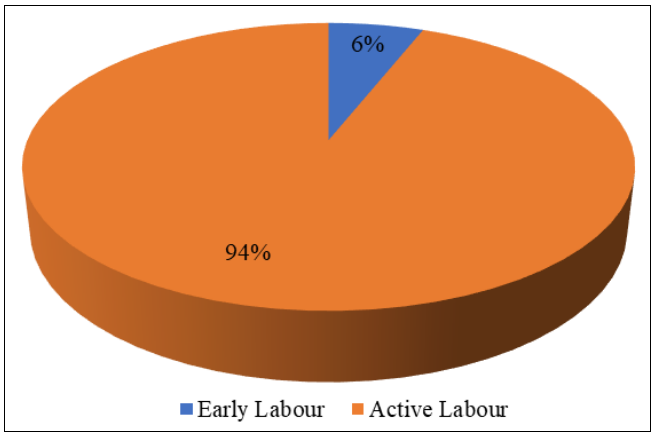
Stages of Labour

In the present study (94%) of patients were in active labour and 6% were in early labour among the study participants. (Table 3 & Fig.2).

Table 3: Stages of Labour

Stages of Labour	Frequency	%
Early labour	3	6
Active labour	47	94

Fig 2: Stages of Labour



Preterm premature rupture of membranes (PPROM)

The PPROM occurred in 34 % of women which was observed only in ≥31 Weeks of gestational age group (Table 4). The gestational age <30 weeks did not show any PPROM.

Table 4: PPROM status and gestational age

Gestational Age	PPROM	
	Present	Absent
<30 Weeks	0	33
≥31 Weeks	17	0

Maternal complications

Hypertension was the major maternal complication (18%) observed in the present study (Table 5) and preeclampsia and gestational diabetes were noted as 16 % and 14 % respectively. Fever was observed in 10 % of the study population. However, 42 % of the study participants had no maternal complications (Fig.3).

Table 5: Maternal complications

Complications	Frequency	%
Hypertension	9	18
Preeclampsia	8	16
Gestational diabetes	7	14
Fever	5	10
Nil	21	42

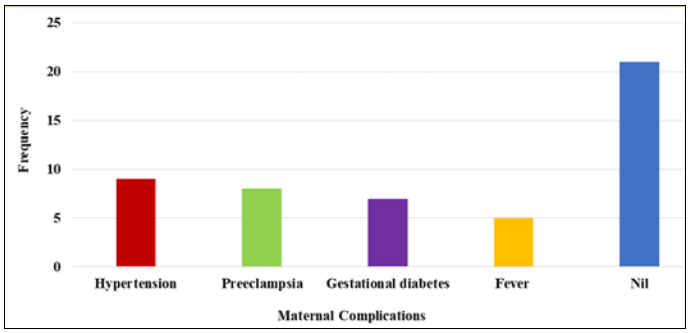


Fig 3: Maternal complications

Thompson Score

The Thompson score revealed that 60 % of the new-born had normal neuronal development whereas, 38 % had mild and 2 % had moderate neuronal abnormalities in the present study (Table 6 & Fig.4).

Table 6: Thompson score status

Thompson Score	Frequency	%
Normal	30	60
Mild neuronal abnormality	19	38
Moderate neuronal abnormality	01	2

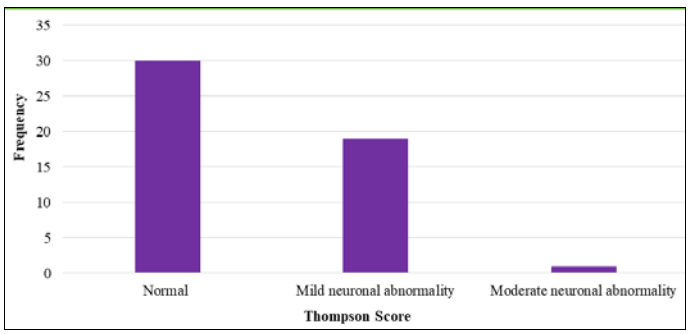


Fig 4: Status of Thompson score

Respiratory Distress Syndrome

The respiratory distress syndrome was observed in 64 % of the new-born in the present study whereas 36 % of new-born did not develop any RDS (Table 7 & Fig.5).

Table 7: RDS Status

RDS	Frequency	%
Present	32	64
Absent	18	36

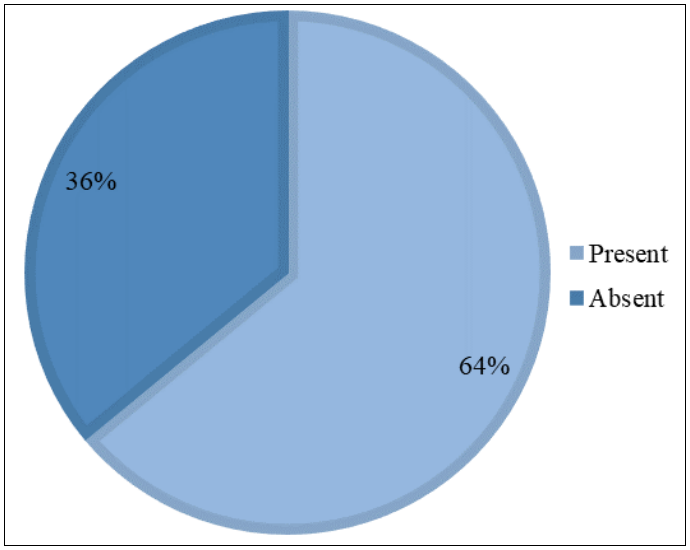


Fig 5: RDS Status

Infusion delivery interval

The infusion of MgSO4 to the preterm mothers and the delivery time was analysed (Table 8). The after infusion of MgSO4, the 80% of delivery occurred after 13 hours was predominant whereas, before 12 hours was only 20 % of preterm mothers (Fig.6).

Table 8: Infusion delivery interval status

Time	Frequency	Mean ±SD
≤ 12 hours	10	5.3±3.16
≥13 hours	40	21.9±3.54

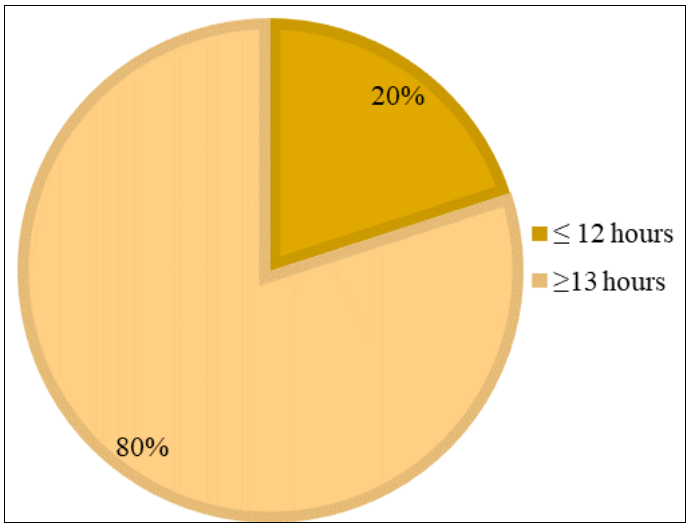


Fig 6: Infusion delivery interval status

APGAR Score

The APGAR score at 1 minute was 5.78±1.64 and at 5 minutes 7.44±1.49 observed in the present study (Table 9 & Fig.7).

Table 9: APGAR Score status

APGAR score	Mean ± SD
At 1 minute	5.78±1.64
At 5 minute	7.44±1.49

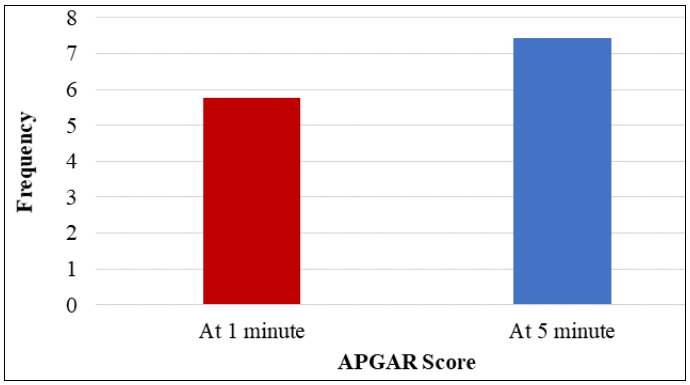


Fig 7: APGAR Score status

Perinatal Outcome

The perinatal outcome was assessed and 8 % of neonatal mortality observed in the present study (Table 10). The remaining 92% of the neonates were normal (Fig.8).

Table 10: Perinatal Outcome

Outcome	Frequency	%
Mortality	4	8
Normal	46	92

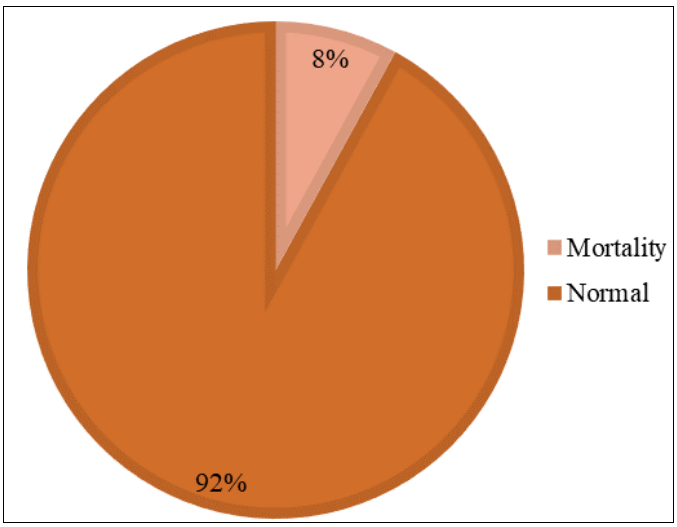


Fig 8: Perinatal Outcome

Discussion

MgSO4 became a standard of treatment for women delivering preterm infants in many institutions. This prospective observational study was conducted in which the individual obstetricians were responsible for the Obstetric management and the neonatal team was responsible for the NICU and clinical treatment of the neonates.

Few earlier studies [17-18] have evaluated the feasibility and safety of using magnesium sulphate for neuroprotection during pregnancy. Ow *et al.* [17] reported a 40% implementation rate in the first 12 months. The study's only evidence on potentially magnesium-related maternal problems was that infusion was discontinued in 2% of women due to adverse symptoms, most

often hypotension. Gibbins *et al*. and, Tan *et al*. [19] implemented a comparable departmental guideline and reported a first-year implementation rate of 51% and 82%, respectively. They, like this present study, reported no incidents of significant adverse maternal consequences.

In earlier trials, the prenatal MgSO4 therapy protocol for fetal neuroprotection included a loading dose of 4–6 g intravenously over 20–30 minutes and a maintenance dose ranging from none to 1 g or 2 g per hour for 12 h or 24 h.[20] Increased loading dose (6 g) and maintenance dose (2 g per hour) were utilized in studies demonstrating unfavorable newborn gastrointestinal outcomes in the presence of antenatal MgSO4 exposure.[27, 28] The total dose of prenatal magnesium sulphate therapy for fetal neuroprotection was more (50.945.7 g or 33.019.8 g) [20, 21] than the dose used in our investigation (Loading dose 4g and maintenance dose 1 g). However, studies that employed a lower dose of MgSO4 (4 g loading dose alone or 4 g loading dose plus 1 g per hour maintenance dose for 24 hours), such as the Australasian collaborative experiment (ACTOMgSO4) and the European Trial (PREMAG), and the current investigation, all followed a similar procedure [21-24]. As a result, it is critical to develop the optimal fetal neuroprotection regimen in order to maximize effectiveness while minimizing detrimental effects on both the fetus and mother, particularly in those at risk of preterm birth at fewer than 26 weeks gestation.

Preterm birth was more prevalent in the 20-35 year age group, which is the most common reproductive age group in this study. A prior study discovered that preterm birth occurred in the age group of 26–34 years (53 percent) [27]. Bansal *et al*., [28] observed that 81% of premature deliveries occurred between 30 and 34 weeks of gestation, emphasizing the importance of focusing our resources on survival in this age group. The current study's findings also corroborated a prior study's observation that 90% of preterm births occur after 31 weeks of gestation.

MgSO4 has been utilized in obstetrics for decades. Despite its familiarity and ease of usage, there are concerns about antenatal MgSO4's potential harmful effects on preterm newborns. Mina Abbassi's study on the newborn effects of MgSO4 in 6654 pre-eclamptic women found that hypotonia, decreased 5-minute Apgar, intubation, and admission to the NICU were all significantly elevated.[28] In a prior study, comparable to the Cochrane systematic review, the five-minute Apgar score<7, which quantifies clinical indications of newborn depression, revealed no difference between the two groups.[29] However, in the current study, the average APGAR score at 5 minutes was 7.44, which contradicts prior study findings. The present study discovered that infants who received prenatal MgSO4 had a lower risk of requiring invasive mechanical ventilation.

A previous study indicated that infant mortality was significantly greater in the MgSO4 group [30] than in the control group [31], but the difference was not statistically significant. All newborn deaths occurred regardless of whether they were exposed to antenatal MgSO4, and hence the adverse effects on neonates may be difficult to link directly to the effects of MgSO4. While Crowther, Magpie, Marret, and Rouse found no significant difference in mortality between infants exposed to prenatal MgSO4 and those not exposed to antenatal MgSO4, Mittendorf found a substantial increase in death in the MgSO4 group compared to the non-MgSO4 group [32-36]. In the present study, infant mortality was 8%.

The previous study found that two newborns with mild encephalopathy survived, whereas the deceased infants had moderate to severe HIE, as measured by increased Thompson scores (p<0.005) and more severe metabolic acidosis (p<0.05). There were no significant changes between the two groups in terms of hemodynamic status, kidney damage, or laboratory cytolysis. Although a continuum exists indicating a rising risk of encephalopathy with increasing acidemia,[37] its positive predictive value, sensitivity, and specificity for predicting brain injury are all known to be low.[38] On the other hand, the Thompson score system has substantial predictive values for neurological outcomes at one year, particularly when the highest value and maintenance of aberrant signals are combined [40]. This score is a straightforward clinical method for assessing encephalopathy in neonates with perinatal asphyxia. It includes a neurological examination, an assessment of respiration and fontanelle tension, and consideration of the most severe signs and their persistence [41]. This strategy is strongly recommended for monitoring HIE newborns and is widely accepted as a good tool for identifying infants at increased risk of adverse outcomes. Additionally, the present study calculated the Thompson score and discovered that 40% of participants had some type of neural abnormalities.

There were no significant associations between the time period from treatment initiation to birth, the total dose received, or whether maintenance medication was received and any of the key health outcomes. Due to the fact that these events all occur after randomization and may be influenced by the therapy administered, caution should be exercised when interpreting the data. With maternal side effects rising with increasing total dose [42] and concerns regarding maternal safety, it may be prudent on a clinical level to limit treatment to times close to delivery and to limit magnesium use to a 4-g bolus loading dosage with or without a 1-g/hour maintenance dose.

Conclusion

Prenatal Magnesium sulphate given for foetal neuroprotection before preterm birth avoids cerebral palsy and lowers the combined risk of fetal/infant death or cerebral palsy. Benefits are evident independently of the cause of preterm delivery, with effects that are consistent across a variety of preterm gestational ages and treatment regimens. If this relatively inexpensive, simple-to-use medication were widely adopted around the world, it would have significant global health advantages for infants delivered prematurely.

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