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# THE EFFECT OF ETHAMSYLATE ON NEONATAL MORTALITY IN PRETERM INFANTS*

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Ethamsylate (diethyl ammonium 1, 4-dihydroxy-3-benzene sulfonate) is a capillary-stabilizing agent which has been demonstrated to decrease the incidence of lesser grades of intraventricular-periventricular hemorrhage in preterm infants. It is assumed that it acts on both platelet and vascular functions by presumably blocking the synthesis of various prostaglandins[1-3].

The objective of the present study was to obtain data regarding the effect that ethamsylate prophylaxis has on the neonatal mortality rate in preterm babies when no cranial ultrasound equipment is available to detect intracranial hemorrhage occurring during the first few days of life which is the main cause of death or neurological sequelae.

## Material and Methods

This study was carried out at the Hacettepe University Children's Hospital Neonatal Intensive Care Unit between January 1986 and November 1987. 246 newborn infants with gestational ages of 34 weeks or less were eligible for the study. Those infants with lethal congenital malformations diagnosed at birth were not included. In our center, each eligible infant was assigned a trial number consecutively and either given or not given ethamsylate.

The study group consisted of 146 infants and the control group 100 infants. Both groups received the same therapy except for ethamsylate which was only given to the study group. Ethamsylate was administered 12.5 mg/kg body weight (0.1 ml/kg body weight from 250 mg/2 ml ampoules) intravenously within an hour after

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delivery, and was followed by 6-hourly doses intravenously for four days (total dose 200 mg/kg body weight).

Neonatal and early neonatal mortality (deaths occurring less than 7 completed days after birth) were calculated in both groups and the results were expressed in percentages. The statistical significance of the differences between the groups were calculated by the Student's *t* test.

**Results**

The effect of ethamsylate on neonatal and early neonatal mortality rates according to gestational ages of infants are shown in Tables I and II. Although it was shown that ethamsylate had a significant effect on reducing neonatal mortality ($p<0.02$) in infants whose gestational ages ranged between 33-34 weeks, there was no significant mortality decrease in infants whose gestational ages were 32 weeks or less ($p>0.05$).

It was also observed that ethamsylate is effective in reducing the early neonatal mortality rate especially in infants whose gestational ages ranged between 33-34 weeks ($p<0.02$).

TABLE I: The Effect of Ethamsylate on Neonatal Mortality

| Gestational age (wks) | Neonatal mortality rate | | |
|---|---|---|---|
| | Control group | Ethamsylate group | |
| 27 - 28 | 12 / 12* (100%) | 6 / 6 (100%) | $p > 0.05$ |
| 29 - 30 | 18 / 18 (100%) | 13 / 13 (100%) | $p > 0.05$ |
| 31 - 32 | 20 / 35 (57.1%) | 11 / 15 (73.3%) | $p > 0.05$ |
| 33 - 34 | 33 / 81 (40.7%) | 14 / 66 (21.2%) | $p < 0.02$ |
| Total | 83 / 146 (56.9%) | 44 / 100 (44.0%) | $p < 0.05$ |

* Number of deaths·number of cases.

TABLE II: The Effect of Ethamsylate on Early Neonatal Mortality

| Gestational age (wks) | Early neonatal mortality rate | | |
|---|---|---|---|
| | Control group | Ethamsylate group | |
| 27 - 28 | 11 / 12* (91.7%) | 5 / 6 (83.3%) | $p > 0.05$ |
| 29 - 30 | 16 / 18 (88.9%) | 7 / 13 (53.9%) | $p < 0.05$ |
| 31 - 32 | 16 / 35 (45.7%) | 7 / 15 (46.7%) | $p > 0.05$ |
| 33 - 34 | 27 / 81 (33.3%) | 10 / 66 (15.2%) | $p < 0.02$ |
| Total | 70 / 146 (48.0%) | 29 / 100 (29.0%) | $p < 0.005$ |

* Number of deaths/number of cases.

## Discussion

Vascular endothelial cells can synthesize prostacycline (PG $I_2$) which is a potent inhibitor of platelet aggregation and a strong vasodilator. In pathological conditions, mural platelet thrombosis forms over an area of destroyed endothelial cells because the subendothelial layer cells cannot produce PG $I_2$. Thromboxane $A_2$ (Tx $A_2$) which is formed and released by the platelets, is a potent aggregating agent and a strong vasoconstrictor which favours thrombus formation. Normal hemostasis is a result of an equilibrium existing between PG $I_2$ and Tx $A_2$[1-3].

It has been suggested that ethamsylate may modify prostaglandin biosynthesis. Although it does not seem to have anti-cyclooxygenase activity, it does inhibit endoperoxide reductase and isomerase, prostacycline synthetase and thromboxane synthetase activity. Ethamsylate may increase platelet adhesiveness with a rise in the availability of local thromboplastin and a reduction in capillary bleeding time. As a result of these events, ethamsylate probably facilitates thrombus formation[4,5].

The effectiveness of ethamsylate in the prevention of periventricular hemorrhage in low birth-weight infants was evaluated by means of a placebo-controlled double-blind study and it has been shown that ethamsylate reduces the incidence and severity of periventricular hemorrhage by regular cranial ultrasonographic assessment in very low birth-weight infants when given soon after birth for a

period of four days[3]. In our study, although we do not know how many infants had intracranial hemorrhages since a portable ultrasound scanner, was not available, it was demonstrated that ethamsylate reduces the total and early neonatal mortality especially in preterm infants whose gestational ages ranged between 33-34 weeks.

It has been suggested that the role of ethamsylate in the prevention of neonatal intracranial hemorrhage may be a prostaglandin-mediated effect at the germinal matrix capillary membrane level[4,5]. It is known that the predisposition to periventricular-intraventricular hemorrhage in preterm infants is related to the presence of a highly vascularized subependymal germinal matrix which contains a major portion of the blood supply of the immature cerebrum, especially prior to 34 weeks gestational age. This vascularized tissue is highly vulnerable to various factors such as hypoxia, acidosis, hypercarbia, hypothermia and infections which are common in premature infants with respiratory distress syndrome and perinatal asphyxia[6,7]. For example, in a study conducted in our hospital on 112 newborns, in which the diagnosis of intracranial hemorrhage was made at postmortem examination, acidosis-hypoxia and hypercarbia were detected in 93.8 percent and 75.5 percent of the patients, respectively[8].

During the past ten years the neonatal infant mortality rate in our hospital, which has the biggest neonatal intensive care unit in the country, has been found to be very high in small infants with 64.8% and 96.0% in infants whose gestational ages ranged between 31-32 weeks and less than 31 weeks, respectively[9]. The main reasons for these high rates are insufficient perinatal care throughout the country and the fact that patients in high risk groups are referred to our birth clinic from other centers. According to hospital records intrauterine hypoxia and fetal malnutrition have been frequently seen among preterm infants[10].

We did not obtain good responses to ethamsylate therapy in this study compared to previous reports because of the conditions existing in our country. Nevertheless, neonatal mortality was reduced especially in premature infants with gestational ages ranging between 33-34 weeks by using ethamsylate. We believe that if the quantity and quality of perinatal care improve, ethamsylate will be much more effective than the results reported in this study.

In conclusion, ethamsylate can be given to preterm infants just after birth in a dose of 12.5 mg/kg body weight intravenously and thereafter in 6-hourly doses for four days resulting in the reduction of early neonatal mortality. The application of ethamsylate may be a very practical approach in treating preterm infants in developing countries.

## Summary

The effectiveness of ethamsylate in the reduction of neonatal mortality among preterm infants is discussed. It has been shown that the use of ethamsylate was effective in preterm infants whose gestational ages ranged between 33-34 weeks, but not in younger infants. Although intracranial hemorrhages in these infants could not be determined because of the unavailability of a portable ultrasound scanner, we recommend ethamsylate prophylactically for all preterm infants in the prevention of intracranial hemorrhage especially in babies in developing countries.

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